SEP 2 9 2004

TPW 1639

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*ADMITTED IN NEW JERSEY ONLY
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September 23, 2004

VIA PRIORITY MAIL
Alan Koller, Ph.D., Esq.
Sr. Assistant General Counsel
Purdue Pharma, LP
One Stamford Forum
Stamford, CT 06901

Re: U.S. Patent Application No. 10/056,347
Entitled: **ANALGESIC COMBINATION OF OXYCODONE AND MELOXICAM**
Euro-Celtique, S.A.
Our Ref. No.: 200.1079CON2

Dear Alan:

We have now received an Office Action for the above-referenced patent application, a copy of which along with related papers are enclosed for your review.

A response to the Office Action is due **November 26, 2004**, although extensions of time are obtainable if necessary.

Absent your instructions to the contrary, we shall prepare a draft response for your review and consideration prior to the due date. On the other hand, if you have any comments or suggestions concerning this Office Action, we look forward to receiving the same.

Very truly yours,

Clifford M. Davidson

CMD:ie
Enclosure

cc: Robert J. Paradiso, Esq.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/056,347	01/25/2002	Ronald M. Burch	200.1079CON2	8306

23280 7590 08/26/2004

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EXAMINER	
CELSA, BENNETT M	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Excel 9-2-04
Pcm 9-2-04
IPM 9-2-04

2-26-05 Office Action Response Due (Deadline Date)
11-26-04 Office Action Response Due (3 Month Date)
10-26-04 Reminder
9-26-04 Send Reporting Letter
CMD/RJP/OI

Office Action Summary	Application No.	Applicant(s)	
	10/056,347	BURCH ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-44,46 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-44,46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/29/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 38-44 and 46-47 are currently pending and under consideration..

Election/Restriction

1. Applicant's election without traverse of Group II (claims 38-44 and 46-47; use in methods of oxycodone and meloxicam) in the correspondence dated 6/14/04 is acknowledged. Applicant's response to non-compliant amendment dated 7/28/04 is acknowledged.

Priority

Applicant should update the cross-reference to parent application which has subsequently issued as a patent.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 38-44 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. US Pat. No. 4,569,937 (2/86), Engelhardt et al. Inflamm. Res. 44:423-433 (1995), Engelhart Brit. J. Rheumatol. 1996:35(suppl.1): 4-12 and Distel et al. Brit. J. Rheumatol. 1996:35(suppl.1):68-77.

Baker et al. teach pharmaceutical compositions for relieving pain in humans or mammals (e.g. mice, rats etc.) comprising a combination of :

a. a narcotic analgesic (preferably oxycodone: see formulations col. 4-8; mice data in col. 8-10; patent claims), or a pharmaceutically acceptable salt thereof; and

b. ibuprofen (a non-steroidal anti-inflammatory drug or NSAID: see col. 1-2), or a pharmaceutically acceptable suitable salt thereof,

in a weight ratio of about 1:800 (e.g. .001:1) to 1:1 (compare to present claim 47: See col. 2)

with oxycodone amounts of about 5 mgs-600mgs (compare to present claim 46).

The Baker reference teaches oral administration (e.g. see present claim 39), which can be coadministered in a "single dosage form" (e.g. see col. 3-8: and present claim 40) or sequentially administered (e.g. as in present claim 42; see i.e. col. 8-9 ; ".. mice are dosed sequentially..."). The Baker et al. reference teach that dose ratios can be adjusted and that the analgesic activity of the combined oxycodone and ibuprofen activity is "unexpectedly enhanced" or synergistic "i.e. the resulting activity is greater than the activity expected from the sum of the activities of the individual components",

thereby permitting "reduced dosages of narcotic analgesics" (e.g. oxycodone) AND which diminishes adverse side effects (e.g. addiction) and toxicity which would result from the otherwise required amounts of the individual drug components" resulting from high dosages of oxycodone or NSAID's such as ibuprofen. See e.g. col. 1-2; col. 3, lines 19-32 (e.g. compare to present 43 and 44 "reduced" active ingredients). Accordingly, Baker would teach the use of therapeutic and subtherapeutic amounts of oxycodone and/or ibuprofen in view of the synergistic nature of the combinations and the desire to reduce the toxicity and/or side-effects of both agents; and as required by the doctor for his/her particular patient., including dosage optimization e.g. dosage overlapping of active ingredients. See e.g. col. 3 where dosage is modified to suit the particular patient.

The Baker analgesic composition differs from that presently claimed in that it fails to teach the substitution of meloxicam for ibuprofen, or alternatively, the further incorporation of (e.g. encompassed by "consisting essentially of") meloxicam into the Baker compositions.

Engelhardt et al. teach that meloxicam, as compared to other NSAID's (e.g. indomethacin, naproxen etc.) in animal models (e.g. rat):

a. was more efficacious when orally administered in a single dose (e.g. anti-exudative effect; more potent ; more prolonged with a better therapeutic range);

b. had good analgesic effect on inflammatory pain; and

c. had fewer side-effects e.g. inhbited both bradykinin-induced bronchospasm; greater GI tolerance. See e.g. abstract and animal data.

Similarly, Engelhardt teaches that compared to other NSAID's meloxicam has an improved safety profile and good tolerability with high and long-lasting anti-inflammatory and analgesic effects in an animal model (e.g. rats). See abstract and animal data.

Further, the Distel et al. reference teaches that meloxicam is a "preferred" NSAID/COX-2 inhibitor (as compared to other NSAID's e.g. piroxicam/naproxen) which in clinical trials is

is efficacious in the treatment of arthritic pain patients (e.g. osteo/rheumatoid arthritis) but has shown to be more safe, with reduced side-effects (e.g. dyspepsia, ulcers, reduced hemoglobin, gastritis etc.). See Distel et al. Abstract and disclosed studies.

Accordingly, one of ordinary skill in the art would have been motivated to substitute meloxicam (a NSAID) for ibuprofen (a different NSAID) in the Baker reference compositions in light of the Engelhardt et al., Engelhardt and Distel et al. reference teachings that meloxicam is at least equally efficacious, but is safer with less side effects (e.g. as compared to othe NSAID's i.e. ibuprofen).

Alternatively, one of ordinary skill in the art would have been motivated to incorporate meloxicam, with its potent analgesia and reduced side-effect, into the Baker ibuprofen/oxycodone compositions in order to reduce the amounts (e.g. therapeutic/subtherapeutic) of ibuprofen/oxycodone in order to avoid the side effects (e.g addiction) or toxicity resulting from ibuprofen/oxycodone. Additionally, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie*

obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker reference analgesic composition by substituting the NSAID meloxicam (for the NSAID ibuprofen) or supplementing Baker's composition with meloxicam in light of the benefits of meloxicam (increased safety/decreased side effect as compared to ibuprofen) as taught by the Engelhardt et al., Engelhardt and Distel et al. references.

4. Claims 38-44 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over as the Baker et al. '937, Engelhardt et al., Engelhardt and Distel et al. References applied to claims 38-44 and 46-47 above, and further in view of Mayer et al. US Pat. No. 5834,479 (11/98).

The teaching of the Baker, Engelhardt et al., Engelhardt and Distel et al. References recited above is hereby incorporated by reference in its entirety.

To the extent that the Baker, Engelhardt et al., Engelhardt and Distel et al. references fail to teach the administration of the analgesia active agent (e.g. meloxicam) "before, ... with, or after" administration of the oxycodone" (particularly before/after) (e.g. see present claim 42) the Mayer et al. reference is cited.

The Mayer et al. reference teaches that analgesia effectiveness of an analgesia active agent (e.g. a NSAID, such as ibuprofen see i.e. table in col. 7) can be "significantly enhanced" by administering (e.g. oral administration) the active agent

"prior to, with or following the administration of an analgesia enhancer" (e.g. a nontoxic NMDA receptor blocker and/or a nontoxic substance that blocks at least one major intracellular consequence of NMDA receptor activation) such as "dextromethorphan", which is the D-isomer of codeine . See e.g. col. 1; patent claims.

Accordingly, the Mayer et al. reference provides motivation to one of ordinary skill in the art to not only co- administer different analgesic agents to achieve enhanced analgesia, but to also administer the NSAID prior or subsequent to the second analgesic agent i.e. an analgesia enhancer, which includes codeine or its derivatives (e.g. dextromethorphan, dextrorphan, oxycodone etc.) .

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker, Engelhardt et al., Engelhardt and Distel et al. reference teachings by administering one of the analgesic active agents (e.g. meloxicam) "before, ... with, or after" administration of the second analgesic agent (e.g. oxycodone) in order to obtain significantly enhanced analgesia.

Cumulative Prior Art:

1. Wojtulewski et al., British J. Rheumatology 1996 : 35 (Suppl.1) : 22-28.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
August 12, 2004

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 200.1079US	SERIAL NO.: 09/154,354 10/056,347
	LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)	APPLICANT(S): Ronald M. BURCH, et al.	
		FILING DATE: September 17, 1998	GROUP: ~~1627~~ 1639

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AA	0 6 5 4 2 6 3	05/24/95	EP (A1)	A61K	31/135		
	AB	0 6 5 4 2 6 3	05/24/95	EP (B1)	A61K	31/135		
	AC	9 7 1 7 9 7 8	05/22/97	WO	A61K	33/00		
	AD	9 7 2 5 9 8 8	07/24/97	WO	A61K	31/495		
	AE	9 7 3 2 8 5 7	09/12/97	WO	C07D	241/104		

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

AF	Dray et al. New Pharmacological Strategies for Pain Relief. Annual Review of Pharmacology &Toxicology. 36, pp. 253-280. (1996).
AG	Brasseur. L. Revue des therapeutiques pharmacolgolques actuelles de la douleur. Drugs,53 Suppl 2, pp. 10-17. (1997)
AH	Rang et al. New molecules in analgesia. British Journal of Anesthesia, 75, pp. 145-156 (1995)
AI	Beaver, WT. Combination Analgesics. American Journal of Medicine. 77 (Suppl 3A), pp. 38-53. (1984).
AJ	Beaver, WT. Chapter 29: Nonsteroidal Antiinflammatory Analgesics and Their Combinations with Opioids. In Evaluation and Treatment of Chronic Pain, 2nd ed., William & Wilkins pp. 363-383. (1992).
AK	Goodman & Gilman's. The Pharmacological Basis of Therapeutics, 9th Edition. McGraw-Hill, New York, pp 535 and 551-552.
AL	Picard et al. Ketorolac potentiates morphine in postoperative patient-controlled analgesia. Pain, 73, 3 pp. 401-406. (1997).
AM	Etches et al. Continuous Intravenous Administration of Ketorolac Reduces Pain and Morphine Consumption After Total Hip or Knee Arthroplasty. Anesthesia & Analgesia, 81 (6), pp. 1175-1180. (1995).
AN	Hodsman et al. The morphine sparing effects of diclofenac sodium following abdominal surgery. Anaesthesia, 42(9), pp. 1005-1008. (1987).
AO	Kaasalainer et al. Developments in the treatment of cancer pain in Finland: The third nation-wide survey. Pain, 70, 2-3, pp: 175-183. (1997).
AP	Sunshine et al. Analgesic Efficacy of a Hydrocodone with Ibuprofen Combination Compared with Ibuprofen Alone for the Treatment of Acute Postoperative Pain. Journal of Clinical Pharmacology, 37 (10), pp. 908-915. (1997).
AQ	Insel. Chapter 27: Analgesic-Antipyretic and Anti-Inflammatory Agents. In Hardman, ed., Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition. McGraw-Hill, New York, pp. 654-655. (1996).
AR	Polisson. Non-steroidal Anti-Inflammatory Drugs; Practical and Theoretical Consideration in Their Selection. The American Journal of Medicine, 100 (Suppl 2A), pp. 2A-31S - 2A-36S. (1996).
AS	Vane, J. Towards a better aspirin. Nature, 367, pp. 215-216. (1994).
AT	Simon, L.S. Nonsteroidal Antiinflammatory Drugs and Their Effects: The Importance of COX 'Selectivity'. Journal of Clinical Rheumatology, 2 (3), pp. 135-140. (1996).

EXAMINER	DATE CONSIDERED 6/30/04

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FORM PTO-1449 (REV. 7-80) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 200.1079US	SERIAL NO.: ~~09/154,364~~ 10/056,347
LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)	APPLICANT(S): Ronald M. BURCH, et al.	
	FILING DATE: September 17, 1998	GROUP: ~~1627~~ 1639

		OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)
	BA	Van Ryn et al. Selective cyclooxygenase-2 inhibitors: pharmacology, clinical effects, and therapeutic potential. Expert Opinion On Investigational Drugs. pp. 609-614. (1997).
	BB	Vane et al. New insights into the mode of action of anti-inflammatory drugs. Inflammation Research. 44, (No.1), pp 1-10 (1995).
	BC	Engelhardt. Meloxicam: A Preferential Inhibitor of COX-2. British Journal of Rheumatology. 34, Abstract Suppl. 1, p. 48. (1995). Abstract.
	BD	Lane, N.E. Pain Management In Osteoarthritis: The Role of COX-2 Inhibitors. Journal of Rheumatology. Vol. 24, Suppl 49, pp. 20-24. (1997).
	BE	Boyce et al. L-745,337: A Selective Inhibitor of Cyclooxygenase-2 Elicits Antinociception But Not Gastric Ulceration In Rats. Neuropharmacology Vol. 33, pp. 1609-1611. (1994).
	BF	Donelly et al. COX-II Inhibitors - a new generation of safer NSAIDS? Alimentary Pharmacology and Therapeutics, 11, 2, pp. 227-236. (1997).
	BG	Wallace, J.L. Nonsteroidal Anti-Inflammatory Drugs and Gastroenteropathy: The Second Hundred Years. Gastroenterology, 112, 3, pp. 1000-1016. (1997).
	BH	Robinson, D.R. Regulation of Prostaglandin Synthesis by Antiinflammatory Drugs. J Rheumatology, 24, Suppl. 47, pp. 32-39. (1997).
	BI	Tannenbaum et al. An Evidence-Based Approach to Prescribing NSAIDS in Muscoskeletal Disease: A Canadian Consensus. Canadian Medical Association Journal, 155, 1, pp. 77-88. (1996).
	BJ	Mehlisch et al. Analgesic Efficacy and Plasma Levels of a Highly Selective Inhibitor of COX-2 (SC-58635, SC) In Patients with Postsurgical Dental Pain. Journal of Clinical Pharmacology, 37, 9, 863. (1997). Abstract.
	BK	Dammann. Selective COX-2 Inhibition: Its Relevance for NSAID-Gastrointesinal Toxicity. Gut, 39, Suppl. 3, A151. (1996). Abstract.
	BL	Penning et al. Synthesis and Biological Evaluation of the 1, 5 -diarylpyrazole class of cyclooxygenase-2 inhibitors: Identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (SC-58635, Celecoxib). Journal Of Medicinal Chemistry, 40(9), 1347-65. (1997).
	BM	Lipsky et al. Outcome of Specific COX-2 Inhibition In Rheumatoid Arthritis. Journal Of Rheumatology, 24 Suppl 49, pp. 9-14. (1997).
	BN	
	BO	
	BP	
	BQ	
	BR	
	BS	
	BT	

EXAMINER	DATE CONSIDERED 6/30/04

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 200.1079US	SERIAL NO.: ~~09/164,354~~ 10/056,347
LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT(S): Ronald M. BURCH, et al.	
		FILING DATE: September 17, 1998	GROUP: ~~1637~~ 1639

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
MM	AH	0 7 3 4 2 7 5	11/04/1997	Australia	C07D	261/08	✓	
	AI							
	AJ							
	AK							
	AL							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	AM	
	AN	
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EXAMINER	DATE CONSIDERED
M. Lucas	4/30/04

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Notice of References Cited	Application/Control No. 10/056,347	Applicant(s)/Patent Under Reexamination BURCH ET AL.	
	Examiner Bennett Celsa	Art Unit 1639	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-4,569,937	02-1986	Baker et al.	514/282
	B	US-5,834,479	11-1998	Mayer et al.	514/289
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Engelhardt et al., Inflamm. Res. 44:423-433 (1995).
	V	Engelhardt, Brit. J. Rheumatology 1996:35 (suppl. 1): 4-12.
	W	Distel et al., Brit. J. Rheumatology 1996:35 (suppl.1):68-77
	X	Wojtulewski et al. Brit. J. Rheumatology 1996:(suppl. 1): 22-28

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Inflamm Res 44: 423–433 (1995)

1023-3830/95/100423-11 $ 1.50+0.20/0

Anti-inflammatory, analgesic, antipyretic and related properties of meloxicam, a new non-steroidal anti-inflammatory agent with favourable gastrointestinal tolerance

G. Engelhardt, D. Homma, K. Schlegel, R. Utzmann, and C. Schnitzler

Department of Pharmacologic Research, Dr. Karl Thomae GmbH, D-88397 Biberach/Riss, Germany

Received 23 March 1995; returned for revision 24 April 1995; accepted by M. J. Parnham 10 July 1995

Abstract. The anti-inflammatory, analgesic and antipyretic properties of the new non-steroidal anti-inflammatory agent, meloxicam, were investigated in a variety of animal models and compared with the properties of piroxicam, diclofenac, indomethacin and several other NSAIDs.

With respect to the total effect of a single oral dose, the anti-exudative effect of meloxicam on carrageenan-induced oedema in the rat exceeded that of all the NSAIDs included in the comparison. Additionally, meloxicam showed the greatest potency of all the compounds examined with respect to adjuvant-induced arthritis in the rat, the granuloma pouch model and the cotton pellet test in the rat. Unlike indomethacin, in the carrageenan pleurisy model in the rat, meloxicam caused both a dose-dependent reduction in exudate volume and also inhibition of leucocyte migration.

Meloxicam showed a strong and lasting effect on inflammatory pain in the rat. Like other NSAIDs, but unlike dipyrone, meloxicam had no effect in the hot plate and tail clamp tests, which are used to identify weak central analgesic effects. Unlike dipyrone and like indomethacin, meloxicam had no effect in a model of visceral distention pain.

In common with other NSAIDs, meloxicam had no influence on the body temperature of normothermic rats in the anti-inflammatory dose range, but did reduce yeast-induced fever in the rat in a dose-dependent manner. Like piroxicam, meloxicam had a uricosuric effect on rats treated with oxonic acid.

Low-dose meloxicam inhibited both bradykinin-induced and PAF-induced bronchospasm in the guinea-pig, but had no effect on acetylcholine-induced bronchospasm.

Piroxicam had greater ulcerogenic effects in the rat stomach than meloxicam.

The therapeutic range of meloxicam in the rat, with regard to inhibition of adjuvant arthritis, was several times greater than that of piroxicam, indomethacin, diclofenac and naproxen.

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Key words: Meloxicam – Non-steroid anti-inflammatory drugs – Anti-inflammatory activity – Analgesic activity – Gastrointestinal tolerance

Introduction

Meloxicam is a new non-steroidal anti-inflammatory drug (NSAID) with a pharmacodynamic and pharmacokinetic profile which appears to differ from that of conventional NSAIDs. The compound was selected from more than four hundred acidic enol carboxamide derivatives in a programme to optimise platelet inhibitory activity or anti-inflammatory/anti-arthritic activity against gastrointestinal tolerability while maintaining a good pharmacokinetic profile. We were however, unable to separate antithrombotic activity from ulcerogenic activity, since both effects are now known to be associated with inhibition of constitutive cyclooxygenase (COX-1) [1].

The search for a potent anti-inflammatory/anti-arthritic compound with relatively low ulcerogenic activity in the rat stomach and a favourable pharmacokinetic profile was successful. The lead compound meloxicam, was found to inhibit preferentially cyclooxygenase-2 (COX-2). In vitro, meloxicam is 3 times more effective against the inducible COX-2 of cultivated guinea pig peritoneal macrophages than against the constitutive COX-1 of these cells [2]. All other NSAIDs tested in this system were more effective against COX-1 than COX-2. In the rat in vivo, meloxicam was 14 times more potent as an inhibitor of PGE_2-biosynthesis in pleural exudate than as an inhibitor of intragastric PGE_2-biosynthesis. All other NSAIDs tested were more potent inhibitors of PGE_2-biosynthesis in the rat stomach than in the pleural exudate [3]. Meloxicam showed a favourable pharmacokinetic profile which is very similar in rat and man ($t_{1/2}$ man: 20 h; rat: 16 h; plasma protein binding rat and man: 99.5–99.7%; Cl rat and man: 0.11 ml/min/kg) [4, 5]. The introduction of a methyl group into the N-heteroarylcarbamoyl side chain of the molecule facilitated excretion

compared with structurally related compounds. Only the parent compound shows biological activity [6].

The aim of these present studies was to compare meloxicam with well-known NSAIDs in relation to their characteristic pharmacodynamic effects.

Materials and methods

Compounds

Meloxicam, piroxicam, tenoxicam, tenidap and naproxen were synthesized in the laboratories of Boehringer Ingelheim and analytical identity and purity were proven.

Diclofenac (Ciba-Geigy), indomethacin (Agrar), acetylsalicylic acid (Bayer AG), hydrocortisone (Hoechst AG), dexamethasone (Roussel-Uclaf), paracetamol (Bayer AG), dipyrone (Hoechst AG), aminophenazone (Sigma) and codeine phosphate (Boehringer Ingelheim) were commercially obtained.

Animals

The animals used were Chbb:THOM(SPF) rats, Chbb:NMRI(SPF) mice and DHP-guinea-pigs of our own colony. The animals were kept in a 12 h light-dark cycle at 21.5 ± 1.0 °C and 60 ± 10% relative humidity. The animals were given Altromin-R or Altromin MS3022 food (Altromin GmbH, Lage/Lippe) and water ad libitum.

Experimental conditions

Unless otherwise stated, the following conditions were employed in all experiments. The test compounds were suspended in 1% methylcellulose and administered by gavage or given i.v. as described. Control animals received a corresponding amount of vehicle. Food was withdrawn 16 h before drug administration, and during this period animals received only tap water. Experiments were carried out at constant room temperature and humidity (21.5 ± 0.5 C 60 ± 10% relative humidity).

Anti-inflammatory activity

Inhibition of kaolin-induced oedema of rat hind paw. The animals used were male rats weighing between 125 and 150 g. The maximal sagittal diameter of the paw was determined [7] with the aid of a gauge at a constant pressure of 10–12 g.

Oedema was induced according to Hillebrecht [8] by a subplantar injection of 0.05 ml of 10% kaolin (E. Merck) suspension in 0.85% NaCl solution into the rat hind paw. Test drugs were administered orally at varying dosages 30 min before induction of oedema and swelling measured 5 h later. An ID_{35} (dose inhibiting swelling by 35%) was calculated by linear regression analysis [9] with 95% confidence limits [10].

Inhibition of carrageenan-induced oedema of rat hind paw. Comparison of potency from AUCs from a single oral dose. The experiments were carried out with male rats weighing between 120 and 140 g (10 animals/group). Oedema was induced [11] by subplantar injection of 0.05 ml of a 1% saline solution of carrageenan (Seakam). The thickness of the paw was measured as previously described [7]. Test drugs were administered orally at various times prior to the induction of oedema to obtain a time-response curve. The degree of swelling was measured 3 h after induction of oedema and compared with that found in control animals. The area under the inhibition/time curve was calculated both alone and relative to the dose.

Egg white oedema of the rat hind paw. Rats weighing between 120–150 g were used in this study. Oedema was induced according to Wilhelmi and Domenjoz [12] by subplantar injection of 0.1 ml of a freshly prepared 10% solution of native egg albumin in 0.85% saline solution. Meloxicam (2–16 mg/kg), indomethacin (4–16 mg/kg) and hydrocortisone (20–80 mg/kg) were administered orally at 4, 3 and 3 dose levels, respectively, 3 h before oedema induction. Oedema was measured 1 h after induction. ID_{35} was calculated by linear regression analysis [9] with 95% confidence limits [10]. Ten, 20 and 20 rats were employed for the meloxicam, indomethacin and hydrocortisone groups respectively.

Anti-exudative effect measured by the granuloma pouch technique. A modification of the technique of Selye [13] was employed. Male rats weighing between 145 and 170 g were used. 1.0 ml of 1% solution of croton oil (Sigma) in sesame oil was injected, under phenobarbital anaesthesia in an air pouch of 25 ml.

Test drugs were administered orally on 14 consecutive days starting on the date on which the croton oil was administered. On the third day after application of the air pouch, the air was removed by puncture. On the 15th day the animals were killed and the amount of exudate determined. The ID_{20} (the dose which inhibited exudation by 20%) was calculated by linear regression analysis [9] with 95% confidence limits [10] from the exudate volumes found. Nineteen to 20 animals were employed for each drug group. Five, 3 and 5 dose levels were used for meloxicam (0.125–2.0 mg/kg), indomethacin (0.5–2.0 mg/kg) and hydrocortisone (2.5–40 mg/kg) respectively.

Adjuvant arthritis in the rat. Male rats with a mean weight of 210 g were used. Adjuvant arthritis was induced by subplantar injection into the right hind paw of 0.1 ml of a 1% suspension of heat-killed mycobacteria (M. butyricum Difco) in paraffin oil [14]. The volume of both rat hind paws was measured plethysmographically [15] at the beginning of the experiment and on the 21sf day after induction of arthritis. Various doses of the test drugs were administered orally once daily from day 1 to day 21 of the study. The mean increase in paw volume of treated animals was compared with that of controls. ID_{50} values (the dose which inhibited the increase in paw volume by 50%) were calculated by regression analysis [9] with 95% confidence limits [10].

Leucocyte migration and exudate formation in carrageenan induced pleurisy in the rat. The experiments were carried out in male rats weighing between 350 and 400 g. Pleurisy was induced according to Vinegar *et al.* [16] by intrapleural injection of 0.5 ml of a 2% sterile solution of carrageenan (Seakam) in 0.9% NaCl solution under ether anaesthesia on the right side of the mediastine between the 4th and 5th rib. The test drugs were administered orally 2 h before induction of pleurisy.

Twenty-four hours after administration of carrageenan, the animals were killed by an overdose of ether, the pleural exudate collected and the pleural cavity washed with 2 ml of 0.9% saline (containing 5 IE heparin/ml). The exudate volume was recorded, and the total cell number determined in a Coulter counter. Exudate cells were sedimented by centrifugation, resuspended in 0.15 ml of homologous rat serum, stained on slides and differential counts of at least 200 cells per preparation were determined. Animals with an exudate contaminated with erythrocytes were omitted from the experiments.

Granuloma formation. A modified cotton pellet test [17] was employed. Cotton pellets (dental wadding rolled into a ball) were impregnated with 0.05 ml of a solution of 1% carrageenan in water and dried. Male rats weighing between 110 and 125 g were used. Cotton pellets weighing 12–14 mg were implanted into the subcutaneous space in the scapular region (2 pellets on each side).

Test drugs were administered orally once daily for successive days, starting on the day of implantation. On day 8 after implantation, the animals were killed by an overdose of ether and the granulation tissue and cotton pellets removed. The cotton pellets were weighed after drying at 60°C for 24 h and the inhibition of the increase in dry weight measured.

Analgesic activity

Inflammatory pain in the rat. A modification of the method of Randall and Selitto [18] was employed using an analgesimeter (Basile).

For this experiment male rats weighing 100–130 g were used. A freshly prepared suspension of 1.12 g freeze-dried yeast (Oetker) in 18.9 ml of 5.55% glucose solution in water was injected subplantarly into the right hind paw under ether anaesthesia. The injection volume was 0.1 ml. Three to five doses of each compound were tested and groups of 10 rats were used for each dose. The pain threshold was measured in g of contact pressure 3 h after subplantar administration of the yeast suspension. Test substances were administered orally 90, 180 and 360 min and 18 h before pain measurement. An ED_{150} (i.e. the dose raising the pain threshold by 50%) was calculated by linear regression analysis [9] with 95% confidence limits [10].

Heat-induced pain (hot plate technique) in the mouse. A modification of the method of Chen and Beckman [19] was employed, using a 3 mm thick aluminium plate with a surface temperature of 52.0 ± 0.1 °C as a hot plate. Male mice weighing an average of 20 g were employed in this experiment. The animals were exposed to the hot plate before and after oral administration of the test drugs in a range of doses and the reaction time measured. Where the individual reaction time after treatment was extended by more than 100% of the value before treatment, the animal was classified as analgesic. As far as possible, an ED_{50} was calculated by probit analysis [20] with 95% confidence limits from the percentage of animals that were classified as analgesic after receiving the test drugs.

Mechanically induced pain (tail clamp test) in the mouse. Haffner's [21] tail clamp method was employed using a Dieffenbach clamp which exerted a pressure of 350–400 g on the tail root.

Male mice weighing 18–24 g were checked before treatment for unmistakable defence reactions to the clamp. After treatment, the numbers of animals which no longer reacted to the clamp were determined at intervals of 30 min. ED_{50} was calculated by probit analysis [20], with 95% confidence limits on the basis of the percentage of mice that did not show nociceptive reactions after receiving the test drugs orally in a range of doses.

Visceral pain reflex of the rat

Male rats weighing between 320–350 g were anaesthetized by intraperitoneal injection of 45 mg pentobarbital-Na/kg. The trachea was cannulated and blood pressure recorded from a carotid artery via a Statham transducer. Test compounds were injected intravenously via a catheter in the jugular vein.

According to the method of Lembeck and Skofitsch [22], a 10 cm segment of the upper jejunum was ligated. On the distal end of the segment a catheter was inserted and connected with an infusion pump and a Statham transducer. Dilation pain was provoked by an infusion of warmed (37 °C) 0·9% saline into the lumen of the jejunum segment until a rise of pressure up to 80 mmHg was obtained in the lumen.

Test compounds were administered as a solution in 0.9% saline i.v. A volume of 0.5 ml/100 g was injected during a period of 60 sec. As far as possible an ID_{50} was calculated by linear regression analysis [9] with 95% confidence limits [10] from the diminution of the fall in diastolic blood pressure provoked by the dilation of the jejunum segment.

Antipyretic activity

Body temperature of normothermic rats. The course of rectal temperature of male rats weighing between 120–150 g was monitored continuously by thermoelements (Philips) and the maximal temperature reduction obtained for each animal compared to its baseline temperature.

From the mean temperature depression resulting from oral administration of various doses of the test substances, an $ID_{-1.5\,°C}$ (i.e. the dose reducing body temperature by 1.5 °C) was calculated, where possible, by linear regression analysis [9] with 95% confidence limits [10].

Yeast fever in rats

Yeast fever [23] was induced by subcutaneous administration of 1 g/kg freeze dried baker's yeast (Oetker) as a 20% suspension in 0.9% saline solution. Four hours after administration of the yeast, the test drugs were administered in methylcellulose by gavage (1.0 ml/100 g). Body temperature was measured 2 h later as described for normal rats. The $ID_{-1.0\,°C}$ (i.e. the dose lowering the body temperature by 1 °C within 2 h) was calculated by linear regression analysis [9] with 95% confidence limits [10].

Uricosuric effect in rats

Test drugs were administered orally to rats weighing between 140–170 g together with 125 mg/kg potassium oxonate (Sigma) in 1% methylcellulose at a volume of 1.0 ml/100 g. Potassium oxonate is an inhibitor of urate oxidase, and therefore raises the blood level of uric acid [24]. Two hours after administration of the test drugs, the animals received 4 ml/100 g tap water by stomach tube. Four hours later an additional 5 ml/100 g water was given. Urine was collected for 24 h following dosing. The uric acid in the urine was assayed by the colorimetric phosphotungstic acid method [25] using Boehringer Ingelheim Diagnostica reagents. A spectrophotometer was used at 560 nm for photometric measurement against uric acid standards.

An ED_{150}, (i.e. the dose which raises the excretion of uric acid by 50%) was calculated from the amounts of uric acid excreted by linear regression analysis [9] with 95% confidence limits [10].

Effect on bronchospasm

Inhibition of bradykinin-induced bronchospasm in the guinea-pig. A modification of the method of Konzett and Rössler [26] was used. Guinea-pigs of both sexes weighing between 400 and 800 g were anaesthetized with urethane and artificially respirated. Bronchospasm was induced according to Collier and Shorley [27] by i.v. injection of 10 µg bradykinin(Sigma)/kg in 0.9% saline solution at intervals of 30 min. The test drugs were administered intraduodenally (0.2 ml/100 g in 1% methylcellulose) 30 min prior to a second administration of the bronchoconstrictor. An ID_{50} (the dose which causes a 50% decrease in bronchospasm) was calculated by linear regression analysis [9] with 95% confidence limits [10].

Inhibition of PAF-induced bronchospasm of anaesthetized guinea-pigs. The procedure was as described above. The bronchospasm was induced by i.v. injection of 20 ng PAF(Sigma)/kg in 0.9% saline solution at intervals of 15 min. The test drugs were administered i.v. (0.05 ml/100 g) in the same vehicle 5 min prior to administration of the bronchoconstrictor. ID_{50} was calculated as described above.

Inhibition of acetylcholine-induced bronchospasm in anaesthetized guinea-pigs. The procedure was as described above. Bronchospasm was induced by i.v. injection of 20 µg acetylcholine(Hoffmann-La Roche)/kg in 0.9% saline solution at intervals of 15 min. Test drugs were administered i.v. in the same vehicle (0.05 ml/100 g) 5 min prior to the administration of the bronchoconstrictor. ID_{50} was calculated as described above.

Ulcerogenic effect on the stomach of the rat

Male and female rats weighing 130–150 g were used in the study. Test drugs were administered orally once daily for three successive days. Four hours after the final administration, the animals were killed by an overdose of ether and the stomach and the duodenum dissected out. ED_{50} was calculated by probit analysis [19] with 95% confidence limits from the percentage of animals that showed at least one gastric ulcer or one haemorrhagic erosion.

Results

Anti-inflammatory activity

Inhibition of kaolin-induced oedema of rat hind paw. This test measures the maximal activity of a compound, but does not take into account its duration of action. The ID_{35} values show that meloxicam had approximately the same activity as piroxicam, indomethacin and diclofenac. However, higher doses of naproxen were required to show the same effect (Table 1).

Inhibition of carrageenan-induced oedema of rat hind paw. Comparison of potency from AUCs from a single oral dose. The AUCs, corrected for dose of compound (mg) and body weight (kg), of meloxicam, piroxicam, indomethacin, diclofenac, tenidap, naproxen were 264, 144, 84, 59, 33, 44% inhibition × h/mg/kg respectively. Figure 1 shows the AUCs resulting from single oral doses of meloxicam, piroxicam, tenidap and naproxen.

Similar peak effects were observed with all the test compounds. However the inhibition/time curves show that a single oral dose of meloxicam produces a more prolonged effect than the other test drugs. Thus, the area under the curve representing the anti-exudative activity of 1.0 mg meloxicam/kg against hind paw oedema of the rat exceeds that of the other test drugs.

Egg white oedema of the rat hind paw. Egg white oedema of the hind paw of the rat was dose-dependently inhibited by hydrocortisone. The ID_{35} of hydrocortisone was 42.0 mg/kg. Like indomethacin, meloxicam in doses up to 16 mg/kg showed no effect against this type of oedema.

Anti-exudative effect measured by the granuloma pouch technique. In this test NSAIDs exert a lower maximum anti-exudative effect than corticosteroids and this is true of meloxicam (Figure 2). In terms of ID_{20}, meloxicam seemed to be twice as active as indomethacin and eight times as active as hydrocortisone (ID_{20} was 0.50, 1.04 and 4.29 mg/kg for meloxicam, indomethacin and hydrocortisone respectively). However the slope of the dose response curve of meloxicam was less steep than that of indomethacin and hydrocortisone. Therefore it was not possible to calculate the relative potency exactly.

Adjuvant arthritis in the rat. Table 2 and Figure 3 show the effects of the test compounds on the adjuvant-induced primary and secondary inflammatory reactions.

Meloxicam, like the other NSAIDs tested, exerted a dose-dependent inhibitory effect on both the primary reaction induced by the adjuvant and also on the

Table 1. Effects on hind paw oedema of rats induced by kaolin 5.5 h after oral administration.

Test substance	No. of dose levels	Dose range* [mg/kg]	No. of animals/dose	ID_{35} [mg/kg]	95% Confidence limits	Regression coefficient
Meloxicam	4	1–8	10	3.35	2.93–3.91	34.5
Piroxicam	5	0.5–8	10	2.71	2.30–3.25	30.8
Indomethacin	3	2–8	10	3.42	2.39–4.49	31.4
Diclofenac	4	2–16	9–10	4.03	3.01–5.08	20.8
Naproxen	4	2.5–20	15	6.25	5.46–7.11	34.1

* used for calculation.

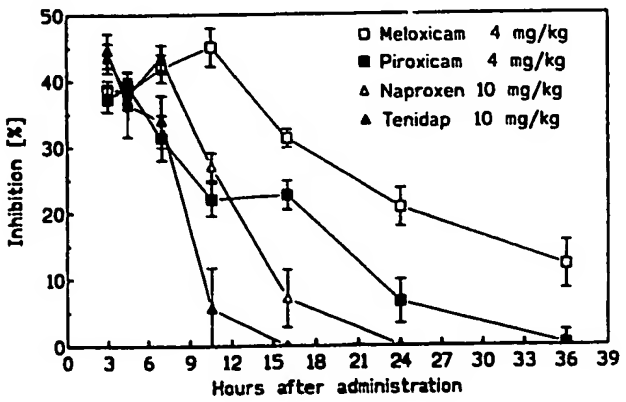

Fig. 1. Percentage inhibition (mean ± SE) of carrageenan oedema in the hind paw of the rat induced by a single oral dose of test compounds.

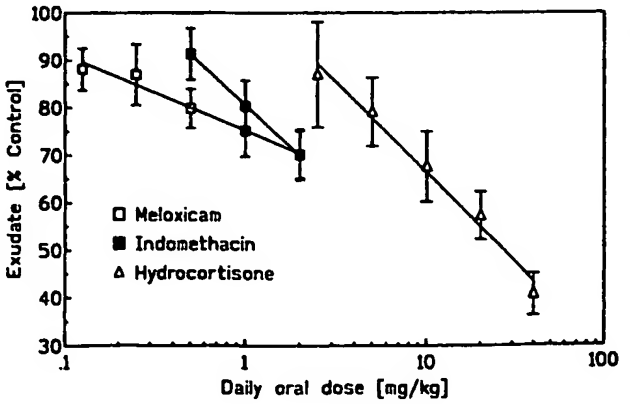

Fig. 2. Anti-exudative effect in the granuloma pouch test in rats after oral administration of test compounds. Mean (±SE) exudate as a percentage of control.

Table 2. Effect on adjuvant-induced primary and secondary inflammatory reactions after daily oral administration of the test compounds for 21 days.

Test compound	No. of dose levels	Dose range [mg/kg]	No. of animals/ dose	Primary reaction		Secondary reaction	
				ID_{50} [mg/kg/day] (95% confidence)	Regression coefficient	ID_{50} [mg/kg/day] (95% confidence limits)	Regression coefficient
Meloxicam	4	0.063–0.5	20	0.17 (0.14–0.21)	38.2	0.12 (0.09–0.14)	45.9
Piroxicam	4	0.2–1.6	19–20	0.61 (0.49–0.78)	46.8	0.67 (0.50–0.95)	69.0
Diclofenac	4	0.2–1.6	20	0.97 (0.75–1.36)	29.2	1.24 (0.84–2.68)	47.4
Naproxen	3	8–32	14–15	14.3 (10.1–18.8)	47.9	11.8 (8.12–14.9)	54.0

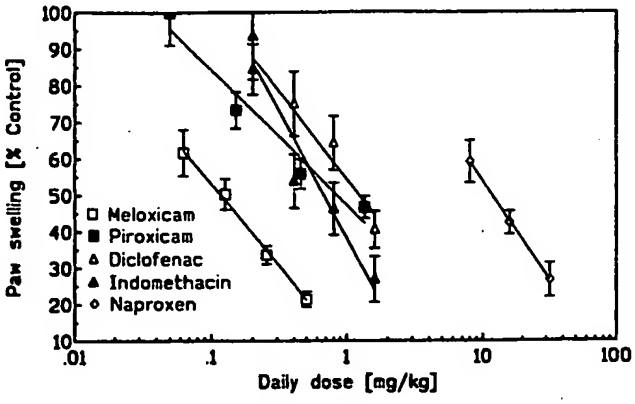

Fig. 3. Inhibitory effect on adjuvant-induced secondary inflammatory reaction (oedema formation) of the hind paw of the rat after oral administration once daily for 21 days.

immunologically-mediated secondary reaction. The ID_{50} values suggest that it is more potent than the other drugs tested.

Leucocyte migration and exudate formation in carrageenan induced pleurisy in the rat. Table 3 shows the volume of exudate and the number of cells in the exudate 24 h after induction of pleurisy. Meloxicam caused a dose-dependent inhibition of exudate formation and migration of PMNs and monocytes. The oral dose of piroxicam required for equal effects on leucocyte migration was about four times higher than that of meloxicam. In contrast, indomethacin showed no influence on leucocyte migration into exudate at doses up to 12 mg/kg. As is usual with corticosteroids, dexamethasone significantly decreased both the volume of exudate and its cell counts, the inhibition of exudate formation being more pronounced than of cell migration.

Granuloma formation. Meloxicam showed a dose-dependent inhibition of the increase in dry weight of the cotton pellets. It appeared to be a more potent inhibitor of foreign body granuloma formation than the other compounds tested (Table 4). Diclofenac did not demonstrate dose dependency. However, the differences between the dry weight of the pellets of control animals and that of all treated rats were statistically significant.

Analgesic activity

Inflammatory pain in the rat. Table 5 and Figure 4 show the ED_{150} values calculated at different time points after oral administration of the test compounds. In the early phase (i.e. 90 min after oral administration), meloxicam, piroxicam and tenidap showed similar effects on inflammatory pain in the rat.

However, the analgesic effect of meloxicam was maintained for 6 h, falling by approximately 50% only during the next 12 h. By comparison, the effects of the other drugs tested were much more transient. Only 180 min after a single dose, the analgesic effects of indomethacin and diclofenac fell to approximately 50% of the initial maximum effect. The effects of piroxicam and tenidap also showed a more rapid diminution than those of meloxicam.

Table 3. Exudate volume and number of cells in the exudate 24 h after induction of pleurisy.

Test compound	Dose [mg/kg]	n	Exudate volume [ml]	Number of cells × 10^6	PMNs × 10^6	Monocytes × 10^6
Controls	–	44	5.00 ± 1.31	158.9 ± 31.7	91.2 ± 24.7	53.2 ± 17.6
Meloxican	4	10	3.34 ± 0.63*	117.2 ± 30.3*	71.5 ± 26.9*	42.5 ± 11.1
	8	10	2.98 ± 1.72*	104.7 ± 15.1*	66.5 ± 19.7*	36.2 ± 11.2*
Piroxicam	4	8	5.20 ± 1.22	146.4 ± 51.2	88.2 ± 36.3	55.1 ± 14.6
	8	9	4.41 ± 1.05	140.7 ± 20.7	85.1 ± 10.5	48.7 ± 18.6
	16	8	4.25 ± 1.55	117.5 ± 43.5*	68.2 ± 29.8*	43.0 ± 10.4
Indomethacin	3	11	4.41 ± 1.24	175.8 ± 44.7	101.5 ± 27.5	71.2 ± 21.4
	6	8	4.82 ± 1.23	156.3 ± 45.8	96.7 ± 35.6	57.0 ± 28.7
	12	7	4.28 ± 0.68	156.6 ± 47.9	96.6 ± 29.2	55.7 ± 21.1
Dexamethasone	0.1	10	2.30 ± 1.22*	103.9 ± 33.9*	64.8 ± 22.5*	36.7 ± 16.4*
	0.3	8	1.43 ± 0.78*	83.1 ± 17.6*	53.3 ± 12.9*	28.3 ± 8.5*

* $p =< 0.05$ (compared to control) (t-test).
Values are means ± standard deviation.

Table 4. Antiproliferative activity measured by the cotton pellet test in rats after once-daily oral administration of test substances for 8 days.

Test compound	Dose [mg/kg/day]	No. of pellets	Pellet weight [%][1)]	Inhibition of increase in dry weight [%]
Control	–	120	214.9 ± 60.7	–
Meloxicam	0.1	80	188.6 ± 45.2*	12.2
	0.2	80	172.8 ± 63.6**	19.6
	0.4	80	143.9 ± 55.0**	33.0
	0.8	80	127.8 ± 52.9**	40.5
Piroxicam	2.0	40	170.3 ± 67.3**	20.7
	4.0	40	130.2 ± 54.1**	39.4
Diclofenac	2.0	40	160.4 ± 46.7**	25.4
	4.0	40	164.4 ± 68.0**	23.5
	8.0	40	158.3 ± 87.2**	26.3
Indomethacin	2.0	32	171.1 ± 36.9**	20.4
	4.0	32	178.4 ± 52.9**	17.0

* $p =< 0.01$ ** $p =< 0.001$ (compared to controls by t-test after normalization of data).
1) pellet dry weight as a percentage of weight of implanted pellet given as means ± standard deviation.

Table 5. Effect against inflammatory pain in rats following a single oral administration of the test compounds.

Test compound (Dose range mg/kg)	ED_{150} [mg/kg] (95% confidence limits) after oral administration of test drugs			
	90 min	180 min	360 min	18 h
Meloxicam (2–16)	5.64 (5.00–6.36) [R.C.: 81.8]	6.30 (5.61–7.11) [R.C.: 79.2]	6.14 (5.47–6.93) [R.C.: 78.9]	15.7 (12.6–21.4) [R.C.: 50.3]
Piroxicam (4–64)	6.06 (5.24–6.86) [R.C.: 75.6]	8.37 (7.20–9.56) [R.C.: 108.1]	13.3 (11.6–15.5) [R.C.: 61.5]	89
Tenidap (2.5–80)	5.00 (4.35–5.93) [R.C.: 89.4]	7.34 (6.14–8.64) [R.C.: 121.9]	40.1 (36.1–45.1) [R.C.: 54.5]	>80
Diclofenac (1–32)	2.23 (1.91–2.70) [R.C.: 71.2]	3.87 (3.40–4.49) [R.C.: 72.9]	7.67 (6.67–8.99) [R.C.: 67.9]	>32
Indomethacin (1.5–24)	3.09 (2.83–3.38) [R.C.: 114.8]	7.62 (6.84–8.64) [R.C.: 100.3]	13.0 (11.9–14.2) [R.C.: 134.4]	>24
Naproxen (5–40)	11.0 (9.26–12.8) [R.C.: 86.5]	13.5 (10.8–16.6) [R.C.: 91.0]	20.3 (16.9–24.4) [R.C.: 90.4]	>40

R.C. = Regression coefficient.

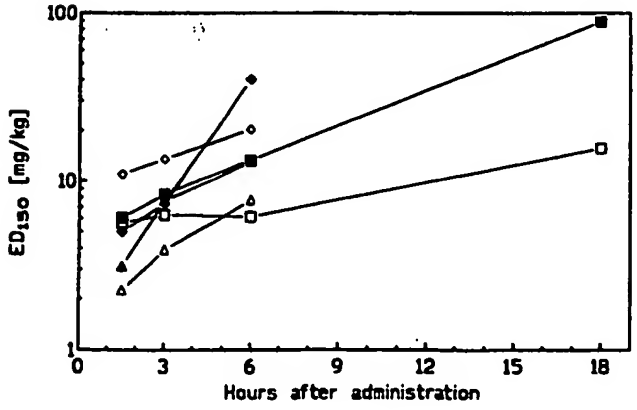

Fig. 4. Inhibition of inflammatory pain in rats following a single oral administration (ED_{150}-values). □ Meloxicam, ■ Piroxicam, △ Diclofenac, ▲ Indomethacin, ◇ Naproxen, ◆ Tenidap.

Heat-induced pain (hot plate-technique) in the mouse. Paracetamol showed a dose-dependent antinociceptive effect against heat-induced pain in the mouse after oral administration [ED_{50} (95% confidence limits): 365 (327–409) mg/kg]. However, meloxicam and the other NSAIDS tested were ineffective under the same conditions within a relevant dose range higher than the anti-inflammatory dose range.

Mechanically-induced pain (tail clamp test) in the mouse. Non toxic doses of codeine phosphate [ED_{50}: 88 (60–130) mg/kg] and dipyrone [ED_{50}: 286 (211–369) mg/kg], demonstrated dose-dependent antinociceptive effects in this model. However, meloxicam and the other NSAIDs tested had no effect at dose ranges higher than the anti-inflammatory active doses.

Effect on the visceral pain reflex of the rat. While dipyrone

Table 6. Effect on yeast fever of the two rat hours after oral administration of the test compounds.

Test compound	No. of dose levels	Dose range [mg/kg]	No. of animals/dose	$ID_{-1.0°C}$ [mg/kg] (95% confidence limits)
Meloxicam	4	4–16	8–10	9.01 (4.50–19.1)
Piroxicam	4	2–16	11–12	4.54 (3.69–5.45)
Diclofenac	4	1–8	12	1.99 (1.56–2.41)
Naproxen	4	5–40	11–12	8.18 (6.15–10.1)
Paracetamol	3	80–180	10–12	95.5 (70.5–113)
Dipyrone	3	10–40	11	23.0 (18.5–30.0)

Table 7. Urinary excretion of uric acid in rats treated with oxonic acid after oral administration of the test compounds.

Test compound	No. of dose levels	Dose range [mg/kg]	No. of animals/ dose	ED_{150} [mg/kg] (95% confidence limits)	R.C.
Meloxicam	4	2–16	6–12	5.85 (3.65–8.64)	28.9
Piroxicam	4	2–16	6	3.77 (1.02–6.53)	22.5
Indomethacin	3	4–16	6	8.09 (3.67–16.1)	30.2

R.C. = Regression coefficient.

Table 8. Inhibition of bradykinin-induced bronchospasm in the anaesthetized guinea pig after intraduodenal administration.

Test compound	No. of dose levels	Dose range [mg/kg]	No. of animals/dose	ID_{50} [mg/kg] (95% confidence limits)
Meloxicam	3	0.02–0.8	15–17	0.40 (0.30–0.55)
Indomethacin	3	0.5–2.0	7–9	1.03 (0.79–1.37)
Acetylsalicylic acid	3	10–40	10	18.2 (12.3–24.5)
Clenbuterol	3	0.001–0.004	8–10	0.0026 (0.0019–0.0035)

[ID_{50}: 75 (52–205) mg/kg] like codeine phosphate [ID_{50}: 1.1 (0.5–1.4 mg/kg] showed a dose dependent inhibition of the visceral pain reflex of the rat after i.v. administration, meloxicam, like indomethacin, was ineffective under the same conditions within a dose range higher than the anti-inflammatory active doses.

Antipyretic activity

Body temperature of normothermic rats. Like the other NSAIDs tested, meloxicam had virtually no effect on the body temperature of normothermic rats in doses up to 8 mg/kg. In contrast, the analgesic-antipyretics, paracetamol ($ID_{-1.5°C}$: 175 mg/kg), dipyrone ($ID_{-1.5°C}$: 72.3 mg/kg) and aminophenazone ($ID_{-1.5°C}$: 27.3 mg/kg), induced a dose-dependent drop in body temperature.

Yeast fever in rat. The results shown in Table 6 demonstrate a dose-dependent effect of meloxicam in yeast-induced fever in the rat. In this respect, meloxicam showed a relatively low potency, with only about half the activity of piroxicam against yeast fever.

Uricosuric effect in rats

Whereas in man uric acid is the end product of purine breakdown, the rat breaks down uric acid even further to allantoin, via the action of urate oxidase. Uricosuric activity of the test compounds was investigated in rats in which uric acid blood levels had been raised artificially by inhibition of urate oxidase with potassium oxonate. The results of this study are shown in Table 7.

Meloxicam and the other NSAIDs investigated showed a dose-dependent uricosuric effect. Meloxicam had a similar potency to piroxicam and indomethacin. The dose-response curves of meloxicam and indomethacin were steeper than those of piroxicam and therefore precise conclusions regarding relative potency on the basis of ED_{150} are not possible.

Effect on bronchospasm

Inhibition of bradykinin-induced bronchospasm in the guinea-pig. Table 8 summarizes the results obtained in this experiment. Meloxicam, like other NSAIDs, caused a dose-dependent reduction of bradykinin-induced bronchospasm in the guinea-pig. On intraduodenal administration, meloxicam had a similar potency to indomethacin. However, the β_2-selective bronchodilator clenbuterol was much more potent than the NSAIDs tested.

Inhibition of PAF-induced bronchospasm in anaesthetized guinea-pigs. The results are shown in Table 9.

The β-agonist clenbuterol caused a dose-dependent inhibition of PAF-induced bronchospasm at a very low i.v. dose. The effect of meloxicam was less marked but it also inhibited bronchospasm at a relatively low dose. More than fifty-fold higher doses of indomethacin were needed to show the same effect. Under identical condi-

Table 9. Influence of bronchospasm of anaesthetized guinea pigs provoked by i.v. administration of 20 ng PAF/kg after i.v. administration of the test compounds.

Test compound	No. of dose levels	Dose range [µg/kg]	No. of animals/dose	ID_{50} [µg/kg] (95% confidence limits)
Meloxicam	5	12–1000	8–10	148 (71–350)
Indomethacin	5	1250–20000	7–12	7820
Piroxicam	3	2500–40000	6–7	>40000
Diclofenac	3	2500–10000	8–9	>10000
Clenbuterol	4	2–16	9–10	7.24 (3.50–32.4)

Table 10. Comparison of the oral therapeutic indices of test compounds with respect to their ulcerogenic effects on the stomach of the rat and their inhibitory effects on the secondary reaction (swelling) to adjuvant of rat hind paw.

NSAID	ED_{50} ulcer [mg/kg/day]	ID_{50} swelling [mg/kg/day]	Therapeutic index
Meloxicam	2.47 (1.64–3.56)	0.12 (0.09–0.14)	20
Piroxicam	1.07 (0.86–1.41)	0.76 (0.49–1.52)	1.4
Indomethacin	2.35 (1.96–2.82)	0.67 (0.50–0.95)	3.5
Diclofenac	2.71 (2.38–3.09)	1.24 (0.84–2.68)	2.2
Naproxen	11.1 (7.84–15.6)	11.8 (8.12–14.9)	0.9

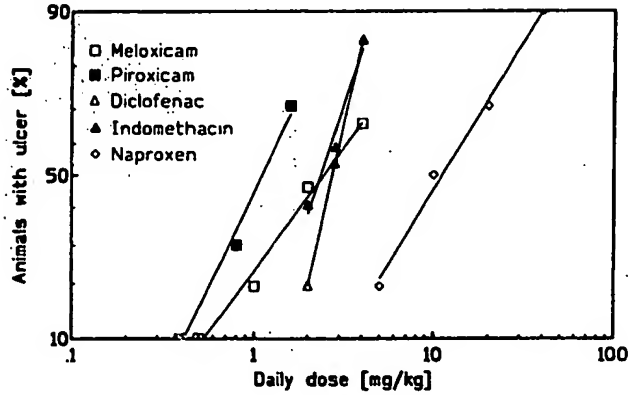

Fig. 5. Ulcerogenic effects on the stomach of the rat after oral administration once daily for 3 days.

tions, piroxicam and diclofenac showed no effect on PAF-induced bronchospasm even at very high i.v. doses.

Inhibition of acetylcholine-induced bronchospasm in anaesthetized guinea-pigs. The β-agonist clenbuterol caused a dose-dependent inhibition of acetylcholine-induced bronchospasm at a very low i.v. dosage. The ID_{50} of clenbuterol was 8.0 µg/kg. Even at very high doses, meloxicam showed no effect against this type of bronchospasm.

Ulcerogenic effect on the stomach of the rat

The results of these experiments are shown in Table 10 and Figure 5. Like other NSAIDs, meloxicam provoked gastricmucosal lesions in a dose-dependent manner. However, the ulcerogenicity of meloxicam in the stomach of the rat was lower than that of piroxicam. On the basis of ED_{50} values, meloxicam, indomethacin and diclofenac showed similar ulcerogenic potentials in the stomach of the rat. In contrast to indomethacin, doses of meloxicam which caused ulceration in the stomach did not cause ulceration in the duodenum or the upper part of the jejunum of the rat.

Therapeutic index in the rat

The therapeutic index was calculated by the ratio of ulcerogenic ED_{50}/anti-inflammatory ID_{50} against the secondary reaction of adjuvant arthritic rat (see Table 10). The therapeutic index of meloxicam was much higher than that of all other NSAIDs tested.

Discussion

The data reported here show that meloxicam differs from classical NSAIDs with respect to its anti-inflammatory, analgesic and antipyretic properties. Most significantly the gastro-intestinal tolerance in relation to the anti-inflammatory potency of meloxicam is much more favourable than that of all other NSAIDs tested.

The anti-exudative effects of meloxicam, as measured in the paw oedema tests, are typical of a cyclooxygenase inhibitor. Whilst kaolin-induced and carrageenan-induced oedema were inhibited dose-dependently, like other NSAIDs [28] meloxicam had no effect on the egg white-induced oedema. The more prolonged effect of meloxicam on carrageenan-induced oedema than the other drugs tested may be due partly to the longer half-life of meloxicam in the rat. There was a good correlation between the plasma concentrations of the drugs and their acute anti-exudative effects in the rat. In contrast to the situation in man, in the young male rat meloxicam has a considerably longer plasma half-life [4] than piroxicam [29].

Adjuvant-induced arthritis in the rat is a model of progressive and destructive joint disease. Since this inflammation is immunologically-mediated, it is similar to the processes of rheumatoid arthritis in man in several aspects. This model permits differentiation between drugs

which have only a symptomatic effect on the acute exudation phase and those which also affect specific immunological events.

Conventional NSAIDs inhibit paw swelling caused by adjuvant-induced arthritis [30]. In Lewis rats meloxicam demonstrates a greater potency against adjuvant-induced arthritis than the other NSAIDs tested [31].

The fact that meloxicam was considerably more potent against adjuvant-induced paw swelling than against exudation in non-specific acute models cannot be explained only by the longer half-life of meloxicam in the rat compared with other NSAIDs. Rather, meloxicam appears to be concentrated in adjuvant-inflamed tissue, since its concentration in hind paws of adjuvant arthritis rats is higher than in the non-inflamed fore legs [32].

It is significant that the effect of meloxicam on the specific secondary reaction to the adjuvant in the contralateral paw, in contrast to the other NSAIDs, is more marked than on the non-specific primary reaction at the site of injection. However, the marked effect of meloxicam on the secondary reaction is probably not due to immunosuppression, since in rats treated exclusively during the early phase of adjuvant arthritis, in contrast to cyclophosphamide, meloxicam only showed weak effects (data not shown).

Even under *in vitro* conditions, and at high concentrations, conventional NSAIDs have little effect on the chemotaxis of neutrophils [33]. At very high doses (10 and 20 mg/kg) piroxicam inhibited PMN and monocyte migration in carrageenan-induced pleural exudate of the rat [34]. The findings reported here confirm these results. Meloxicam had a greater influence on these parameters than piroxicam, but did not achieve the efficacy of the glucocorticoid at a dose which is well tolerated [35].

In the cotton pellet test model used in this study, glucocorticoids show marked dose-dependent inhibition of the growth of granulation tissue [17]. NSAIDs, however, cause only moderate inhibition of connective tissue regeneration [36]. The antiproliferative activity of NSAIDs does not correlate with the antiexudative activity. Meloxicam and piroxicam showed stronger antiproliferative effects than diclofenac and indomethacin. Unlike glucocorticoids, NSAIDs have no effect on existing granulation tissue and only partially inhibit the regeneration of connective tissue [37].

NSAIDs differ from the centrally acting analgesics such as morphine in that their action is mainly peripheral, i.e. at or near the site of the pain production [38]. Like other NSAIDs, meloxicam shows a good analgesic effect on inflammatory pain in the rat hyperalgesia test according to Randall and Selitto [18]. Meloxicam had the most persistent effects of all the compounds investigated.

Like all other NSAIDs, tolerable doses of meloxicam had no effect on heat-induced pain in the mouse (the hot plate technique) or on mechanically-induced pain in the mouse (the tail clamp test). Paracetamol (hot plate test), dipyrone and codeine phosphate (tail clamp test) demonstrated weak central analgesic properties.

The visceral pain reflex model in the rat was originally developed for identification of neurokinin antagonists [22]. More recent observations suggest that substance P receptors in the spinal cord can be inhibited by blocking the spinal cyclooxygenase [39]. In the visceral distension pain model, opiates and dipyrone, effective against colic pain, are also effective. As far as we could observe, even at a high parenteral dose meloxicam did not inhibit this pain reflex in the rat.

The effects of NSAIDs on the body temperature of the mammal differ from that of paracetamol or phenazone derivatives. Unlike these compounds, NSAIDs do not influence the body temperature of the normothermic mammal. They are effective only against pyrogen-induced fever. The effect of meloxicam on yeast-induced pyrexia in the rat is less than that of diclofenac and piroxicam. However, these substances do not constitute an alternative to classic antipyretic agents.

Independently of their anti-inflammatory activity, many NSAIDs are able to increase uric acid excretion [40]. The uricosuric efficacy of meloxicam in rats, in which the uric acid level had been raised through treatment with oxonic acid, was less than that of piroxicam. Thus, meloxicam is not an alternative to the uricosurics currently used in the treatment of gout.

As early as 1960, Collier *et al.* [41] found that acetylsalicylic acid and other NSAIDs are effective inhibitors of bronchospasm induced in the guinea-pig by i.v. doses of bradykinin. The bronchospastic effect of bradykinin is an indirect effect. Bradykinin-induced bronchospasm is mediated by thromboxane A_2 [42].

Unlike piroxicam and diclofenac, even very low i.v. doses of meloxicam had an effect on PAF-induced bronchospasm in the guinea-pig. The inhibition of PAF-induced bronchospasm does not involve receptor antagonism, but inhibition of indirect events. It has been shown that PAF increases the formation of thromboxane A_2 [43] and of LTC_4 [44] in the lung. Meloxicam specifically inhibits bradykinin-induced or PAF-induced bronchospasm in the guinea-pig, therefore, by similar mechanisms shows no general broncholytic properties and has no effect on acetylcholine-induced bronchospasm in the guinea-pig, even at very high doses.

Gastric ulcerogenicity is the dose-limiting side effect of all NSAIDs. The difference between the dose required to achieve the desired effects and ulcerogenic dose is of key importance to the therapeutic use of such a compound. The gastric ulcerogenicity of NSAIDs is predominantly a systemic effect that also correlates with the plasma concentration in man [45].

However, the anti-inflammatory potencies of the known NSAIDs and their gastrointestinal tolerance in patients do not correlate strictly. Large studies have shown that indomethacin and piroxicam at therapeutic doses have a higher risk of gastrointestinal toxicity than most other NSAIDs [46, 47].

The ulcerogenic potential of a NSAID can, in principle, be estimated in short-term tests in the rat. However, the findings of such tests conducted by different investigators can rarely be compared since differences in the methods greatly affect the results. This is clearly shown by the very different data available on the ulcerogenicity of the same substance in the rat stomach, e.g. indomethacin [48, 49]. The scale of the ulceration depends on the animal strain, age, sex, feeding, frequency of administration, evaluation of findings, and calculation

of the ED. The NSAID is administered only once by most investigators. The method we used to evaluate ulcerogenicity is particularly sensitive since the test substances are administered on several consecutive days and an animal is evaluated as positive even if just a single haemorrhagic erosion is identified in the gastric mucosa. By this method it was possible to assess the full efficacy even of compounds which accumulated due to their i.v. longer half-lives. The ED_{50} established for meloxicam in this test was similar to that of indomethacin and diclofenac, but the ulcerogenicity of meloxicam is less than that of piroxicam. This was confirmed by the results of subacute and chronic toxicological studies in rats [50].

The benefit to risk ratio is a measure of the value of a drug. The ulcerogenicity of meloxicam in the rat stomach is mild when measured against anti-inflammatory efficacy in the adjuvant arthritic rat. Since the desired anti-inflammatory potency of meloxicam under the conditions of repeated single daily oral administration (i.e. steady state conditions) to the same species is more than 3 times greater than piroxicam, indomethacin and diclofenac and about 100 times greater than naproxen, at least in the rat, the therapeutic range of meloxicam is 6–20 times higher than that of the other NSAIDs tested.

The pharmacokinetic data for meloxicam in the rat and in man have an unusual similarity [4, 5]. Therefore, it may be assumed that the pharmacodynamic and toxicological findings in the rat can be extrapolated to man.

The pathogenesis of gastric ulcers caused by NSAIDs is complex. There is no doubt that inhibition of biosynthesis of PGE_2 and PGI_2 that protect the mucous membrane and inhibit acid secretion plays a part in the pathogenesis of stomach ulceration caused by NSAIDs [51]. Stable prostaglandin derivatives in animals and man provide protection from gastric ulcers caused by NSAIDs [52]. The efficacy of the different NSAIDs, though, as inhibitors of PG biosynthesis in gastric mucosa are not always in proportion to their peripheral efficacy in the inflammatory exudate [53, 54].

We found that meloixam has a much smaller effect on PG biosynthesis in the mucous membrane of the rat stomach than in the inflammatory exudate in this species and that the resultant increase in gastric acidity is only moderate [3].

In guinea pig peritoneal macrophages in vitro, however, we observed a preferential effect of meloxicam on inducible cyclooxygenase (COX-2) as compared to the constitutive enzyme (COX-1). Piroxicam, tenoxicam, tenidap, indomethacin, diclofenac and flurbiprofen in this model inhibited preferentially the COX-1 [2]. The preferential inhibition of COX-2, therefore, explains the high anti-inflammatory potency in relation to the good gastro-intestinal tolerance of meloxicam.

The clear relationship between the COX-2 selectivity of meloxicam in vitro and its enhanced tolerability in vivo supports selective COX-2 inhibition as a target for therapeutic intervention.

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PHARMACOLOGY OF MELOXICAM, A NEW NON-STEROIDAL ANTI-INFLAMMATORY DRUG WITH AN IMPROVED SAFETY PROFILE THROUGH PREFERENTIAL INHIBITION OF COX-2

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SUMMARY

This review focuses on key pharmacological findings with a new NSAID, meloxicam. Unlike established NSAIDs, it preferentially inhibits inducible COX-2 in guinea-pig peritoneal macrophages and human COX-2 in COS cells. Compared with other NSAIDs, meloxicam is the most potent inhibitor of prostaglandin biosynthesis in pleural and peritoneal exudate, but only a weak inhibitor in the gastric tract and kidney. Ulcerogenicity in the rat stomach is weak in relation to anti-inflammatory potency, resulting in a high therapeutic index. Meloxicam's high anti-inflammatory potency combined with good tolerability can be explained by its preferential inhibition of COX-2. In adjuvant arthritis rats, meloxicam inhibits not only paw swelling, but also bone and cartilage destruction and systemic signs of disease. It inhibits leucocyte migration, but has no effect on leucotriene B4 or C4. Meloxicam shows a long-lasting anti-inflammatory and analgesic effect on inflammatory pain and reduces pyrogen-induced fever, but has no central nervous system effects. The pharmacokinetic profile of meloxicam in the rat is similar to that in man. Metabolites are inactive.

KEY WORDS: Meloxicam, Anti-inflammatory, Cyclooxygenase, Pharmacology, Prostaglandins.

MELOXICAM (Fig. 1) is a new non-steroidal anti-inflammatory drug (NSAID), registered in France. Meloxicam shows a novel pharmacodynamic profile.

Since 1971 [1] it has been generally accepted that the mechanism for both the therapeutic anti-inflammatory, analgesic and antipyretic actions and the common deleterious effects [2] of aspirin-like drugs is mediated through their inhibition of cyclooxygenase (COX), the rate-limiting enzyme in the synthesis of prostaglandins. This action fails to explain why NSAIDs, at equipotent doses, cause different degrees of gastrointestinal (GI) adverse effects [3].

We now know that COX exists in two isoforms [4–6], known as COX-1 and COX-2. The two isoforms have different structures and functions [7–9]. The constitutive COX isoform, COX-1, is involved in processes such as the production of thromboxane A_2 (TXA_2), the production of prostaglandin E_2 (PGE_2) in the kidneys and the production of prostacyclin, which is both antithrombogenic and, in the gastric mucosa, cyto-protective. The undesirable side-effects of NSAIDs on the stomach and kidneys are thought to be due to the inhibition of COX-1 [10]. The beneficial anti-inflammatory effects of NSAIDs are thought to be mediated via the inhibition of the other isoform, COX-2 [10]. The induction of COX-2 by inflammatory stimuli, cytokines or lipopolysaccharides has been demonstrated not only in macrophages [4, 11–15] but also in endothelial cells [13, 16, 17] and synoviocytes [18–21]. The pharmacology of COX-1 is also different from that of COX-2, such that several NSAIDs have been shown to display differential inhibitory activity against COX-2 and COX-1 [22, 23]. Indomethacin, acetylsalicylic acid and piroxicam are more active against COX-1 than against COX-2. This differential inhibitory activity is thought to explain the differing side-effect profiles of current NSAIDs such that those with the highest selectivity for COX-1 tend to provoke most adverse events. Moreover, in principle, a NSAID which displays preferential COX-2 inhibition would be expected to have potent anti-inflammatory effects whilst sparing the patient from treatment-limiting effects, on the gastric mucosa for example. Meloxicam exhibits preferential inhibition of COX-2 over COX-1. A number of other potential selective COX-2 inhibitors are also in the early phases of development. These include: flosulide (CGP-28238), SC-58125, NS-398, L-745,337 and DUP-697.

This review presents the key pharmacological findings for meloxicam, focusing on those which have led to the characterization of meloxicam as a NSAID with an improved safety profile over current treatments through the preferential inhibition of COX-2.

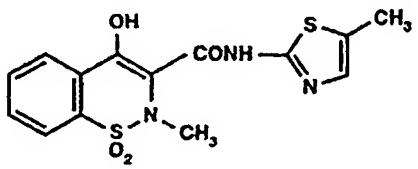

FIG. 1.—Structure of meloxicam.

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EFFECTS OF MELOXICAM

Influence on arachidonic acid metabolism

The *in vitro* and *in vivo* activities of meloxicam and other NSAIDs against COX-1 and COX-2 have been compared in several models.

TABLE I
Influence on COX-1 and COX-2 activity of guinea-pig peritoneal macrophages during 6 h of incubation

NSAID	COX-1 IC_{50} (nmol/l)	COX-2 IC_{50} (nmol/l)	Ratio COX-2/COX-1
Meloxicam	5.8 (4.6–7.2)	1.9 (1.4–2.7)	0.33
Piroxicam	5.3 (3.6–7.4)	175 (149–202)	33
Tenoxicam	20 (5.8–179)	322 (207–489)	16
Tenidap	393 (299–519)	47 800 (39 200–59 700)	122
Indomethacin	0.21 (0.13–0.31)	6.4 (5.0–8.0)	30
Diclofenac	0.86 (0.58–1.17)	1.9 (1.5–2.4)	2.2
Flurbiprofen	15 (8.6–28.2)	4760 (1 270–12 700)	317

*Figures in parentheses are 95% confidence limits.

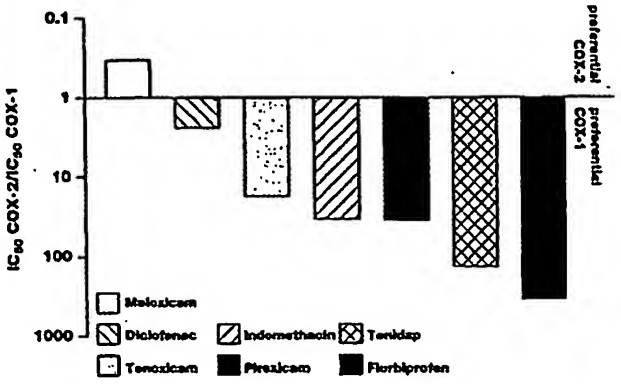

FIG. 2.—Relation of inhibitory activity against COX-1 and COX-2 in guinea-pig peritoneal macrophages *in vitro*. Ratio of IC_{50} against COX-2/IC_{50} against COX-1.

Investigations have been conducted in models where COX-1 and COX-2 expression are induced in animal intact cell systems of guinea-pig macrophages or isolated from cell-free preparations from bovine seminal vesicles, bovine brain or sheep placenta for *in vitro* studies. In addition, effects have been established using human COX-1 and COX-2 transfected into cultured COS-2 cells.

Meloxicam shows weak activity against COX-1 in a cell-free enzyme preparation from bovine seminal vesicles [24, 25], whilst indomethacin is 18 times, diclofenac 29 times and flurbiprofen 45 times more active than meloxicam.

In the intact cell system, indomethacin was the most potent inhibitor of COX-1 activity in non-stimulated macrophages. Meloxicam and piroxicam were more active than flurbiprofen, tenoxicam and tenidap in this cell system (Table I). Lipopolysaccharide (LPS) is used to induce COX-2 and stimulate PGE_2 production in guinea-pig peritoneal macrophages. The differences between the activity of the NSAIDs tested against these two cell models of COX-2 and COX-1 are demonstrated in Table I.

It can be seen from the COX-2/COX-1 inhibitory ratios that there are clear differences between the different NSAIDs in terms of preferential inhibition of one COX isozyme over the other (Table I and Fig. 2). Of all the NSAIDs tested, only meloxicam preferentially inhibited COX-2-induced in LPS-stimulated cells over COX-1 present in non-stimulated cells. Piroxicam, tenoxicam, tenidap, indomethacin and flurbiprofen inhibited the COX activity in non-stimulated macrophages more potently than in LPS-stimulated macrophages. Diclofenac displayed similar activity against COX-1 and COX-2 in these cell models.

These results were confirmed in human COX-1 and COX-2 stably transfected into cultured COS-2 cells. Meloxicam is a selective inhibitor of human COX-2 in this assay system. In contrast, piroxicam, indomethacin, acetylsalicylic acid, naproxen and ibuprofen were either non-selective inhibitors of COX-1 and COX-2 or selective inhibitors of COX-1 [26].

The preferential inhibition of COX-2 by meloxicam is highly dependent on the structure of the drug. Modification of meloxicam to the 4′-isomer (the methyl substitution on the thiazole group is located at position 4 rather than position 5) resulted in a significant loss of selectivity against COX-2. The 4′-isomer showed selectivity for COX-1 [27].

The influence of meloxicam and some other NSAIDs on PGE_2 synthesis in various non-inflamed and inflamed tissues has been investigated *in vivo*. Their differential abilities to inhibit the expression of COX-2 in inflamed areas (pleurisy of the rat, peritonitis of mice) and to influence the activity of constitutive COX-1 in non-inflamed areas such as the stomach, kidney and brain were examined. These investigations are of clinical interest because the acute, noxious effects of NSAIDs, such as decrease in renal blood flow and electrolyte and water retention, are mediated by inhibition of this intrarenal PGE_2 synthesis [28]. Excretion of intact, non-metabolized PGE_2 is a measure for COX-1-induced production of intrarenal PGE_2 [29]. In the gastric mucosa, COX-1 mediates the formation of cytoprotective prostaglandins. Specifically, the inhibition of PGI_2 and PGE_2 synthesis is implicated in the pathogenesis of NSAID-induced gastric ulcers [30].

Pleurisy of the rat was used as a model of the inflammatory process. In this carrageenan-induced model of inflammation, COX-2 is responsible for the production of prostaglandins [31].

All NSAIDs tested lowered the PGE_2 content of the pleuritic exudate from the rat in a dose-dependent manner. Meloxicam was twice as potent as tenoxicam, three times as potent as flurbiprofen and eight times as potent as diclofenac as an inhibitor of COX-2-induced PGE_2 production in this model. Tenidap displayed only weak inhibitory activity against COX-2 [32].

Intrarenal PGE_2 synthesis, mediated by COX-1, was inhibited by all of the NSAIDs tested in a

TABLE II
Influence on PGE_2 content of pleuritic exudate and urine of rats

NSAID	Pleuritic exudate ID_{50} (mg/kg/day)	Urine ID_{50} (mg/kg)	Ratio urine/pleurisy
Meloxicam	0.65 (0.54–0.78)*	1.85 (1.05–2.78)	2.8
Piroxicam	0.85 (0.60–1.09)	0.24 (0.10–0.41)	0.28
Tenoxicam	1.32 (0.14–1.52)	0.62 (0.40–0.94)	0.47
Tenidap	12.8 (9.62–18.0)	0.64 (0.23–1.50)	0.05
Diclofenac	5.06 (3.71–6.62)	1.86 (1.23–2.55)	0.37
Flurbiprofen	2.18 (1.78–2.75)	0.26 (0.11–0.58)	0.12

*Figures in parentheses are 95% confidence limits.

TABLE III
Influence on PGE_2 content of pleuritic exudate and gastric juice of rats

NSAID	Pleuritic exudate ID_{50} (mg/kg/day)	Gastric juice ID_{50} (mg/kg)	Ratio gastric juice/pleurisy
Meloxicam	0.65 (0.54–0.78)	8.99 (7.23–10.3)	13.8
Diclofenac	5.06 (3.71–6.62)	1.64 (1.44–2.05)	0.32
Naproxen	12.7 (9.74–16.6)	3.56 (2.29–6.23)	0.28
Flurbiprofen	2.18 (1.78–2.75)	0.14 (0.10–0.28)	0.064

*Figures in parentheses are 95% confidence limits.

dose-dependent manner. Meloxicam had a similar potency to diclofenac in suppressing PGE_2 excretion. Piroxicam and flurbiprofen displayed the greatest potency of all agents investigated and were eight times as potent as meloxicam [32] (Table II).

PGE_2 content of the rat gastric juice was lowered by all NSAIDs tested in a dose-dependent manner [32]. Meloxicam is only a weak inhibitor of PGE_2 synthesis in the rat gastric mucosa. Diclofenac caused the same effects at one-fifth the dosage, whilst flurbiprofen was the most potent with 64 times the inhibitory activity of meloxicam in this model (Table III).

Consequently, NSAID effects on COX-1 mediated PG production in the gastric mucosa and kidney have been compared with their influence on PG synthesis induced by COX-2 in the rat pleural exudate (Tables II and III) [32]. Such a comparison can be used to characterize each NSAID with respect to renal and gastric tolerability at therapeutic doses. The ratio of the ID_{50} for inhibition of PGE_2 production in the urine to the ID_{50} for inhibition in the pleuritic exudate gives an indication of the relative selectivity of a NSAID for inhibiting COX-2 activity over COX-1 in the kidney. Of all the NSAIDs tested, meloxicam showed the greatest difference between the doses sufficient to inhibit PGE_2 synthesis in the pleuritic exudate and those necessary to inhibit urinary PGE_2 excretion. For meloxicam this ratio was 10 times higher than for piroxicam, eight times higher than for diclofenac and 50 times higher than for tenidap (Table II). Similarly, the ratio of the ID_{50} for inhibition of PGE_2 production in the gastric mucosa to the ID_{50} for the inhibition of PGE_2 production in the pleuritic exudate gives an indication of the gastric tolerance of an agent (Table III). For meloxicam the ratio was 40 times higher than that of diclofenac and naproxen and 100 times greater than that of flurbiprofen.

Further investigations have reviewed the effects of various NSAIDs on COX activity *in vivo* in other tissues such as the brain and serum, and also on inflammatory products of lipooxygenase (another enzyme, distinct from COX, which is active within the arachidonic acid cascade).

In rats and mice, under physiological conditions, a small amount of PGE_2 is present in brain tissue. Following administration of a convulsant dose of pentetrazole to rats and mice, a rapid rise in brain PGE_2 can be observed. In this model the glucocorticosteroid dexamethasone does not inhibit the pentetrazole-induced increase in PGE_2. This indicates that the stimulated PGE_2 synthesis is due to constitutive COX-1 activity. PGE_2 production was dose-dependently inhibited by all of the NSAIDs tested in this model. Meloxicam had the weakest ability to suppress rat brain COX-1, followed by tenoxicam which was three times as potent, indomethacin which was five times as potent and piroxicam which was 10 times as potent. Diclofenac displayed the greatest inhibitory activity against COX-1 and was 20 times as potent an inhibitor as meloxicam [32].

In the serum, COX-1 is the isozyme responsible for formation of thromboxane (TXA_2), which is implicated in platelet aggregation. The effects of each NSAID on the TXB_2 content of rat serum (TXB_2 is the stable metabolite of TXA_2) were once again dose-dependent. Meloxicam, tenidap and indomethacin were weak inhibitors of TXB_2 production compared with tenoxicam and piroxicam. Interestingly, under the same experimental conditions, acetylsalicylic acid, an irreversible inhibitor of platelet COX-1, was still only 15 times less potent than meloxicam [32].

The effect of NSAIDs on the formation of products resulting from the actions of lipooxygenase on arachidonic acid have also been studied. These products are known as leucotrienes, and we specifically looked at the effects of NSAIDs on the production of two types, LTC4 and LTB4. Notably, meloxicam did not affect levels of either LTB4 in the pleural exudate or LTC4 in the mouse peritoneal exudate at concentrations which had previously reduced PGE_2 formation in each inflammatory model. In contrast, indomethacin and tenidap increased the LTB4 content of pleuritic exudate and tenidap increased the LTC4 content of peritoneal exudate in a dose-dependent manner, at doses known to inhibit PGE_2 synthesis [32]. Leucotriene C4 is responsible for mediating some of the symptoms of asthma and thus an agent which raises levels could further exacerbate a pre-existing asthmatic condition.

Caution is commonly expressed against the use of NSAIDs in asthmatic patients.

Anti-inflammatory effects

Standard animal models of inflammation, including carrageenan- or kaolin-induced rat paw oedema, granuloma formation following implantation of cotton pellets in the rat, carrageenan-induced rat pleurisy and rat adjuvant-induced arthritis, have been used to establish the anti-inflammatory effects of meloxicam. In all models meloxicam was able to suppress the inflammation with a single dose producing a prolonged effect [33].

TABLE IV

Anti-inflammatory potency against adjuvant arthritis (inhibition of swelling provoked by the secondary reaction) and ulcerogenic potency in the rat

NSAID	Adjuvant arthritis ID_{50} (mg/kg/day)	Stomach ulceration ED_{50} (mg/kg/day)	Ratio ulcus/arthritis
Meloxicam	0.12 (0.09–0.14)*	2.42 (1.64–3.56)	20
Diclofenac	1.23 (0.84–2.76	2.71 (2.38–3.09)	2.2
Piroxicam	0.77 (0.46–1.71)	1.09 (0.26–1.41)	1.4
Naproxen	11.8 (8.1–14.9)	11.2 (8.1–15.4	0.95
Flurbiprofen	0.97 (0.55–2.16)	0.21 (0.15–0.30)	0.22
Acetylsalicylic acid	198 (169–245)	32.4 (21.1–49.7)	0.16

*Figures in parentheses are 95% confidence limits

Meloxicam's anti-inflammatory activities have been compared with other, established NSAIDs in a rat model of progressive and destructive joint disease. In adjuvant-induced arthritis of the rat the acute symptoms are related to COX-2 expression [18] and inflammation is also immunologically mediated. Meloxicam exhibits greater anti-inflammatory potency than other compounds tested in this model (Table IV and Fig. 3) [33, 34]. At low doses meloxicam prevented not only oedema but also bone and cartilage destruction. In comparison, piroxicam showed similar activity at higher doses whilst diclofenac and tenidap were only weakly active in preventing bone and cartilage destruction at doses which suppressed swelling [34].

As a consequence of immunological reaction in rat adjuvant arthritis, both spleen weight and erythrocyte sedimentation rate (ESR) are increased. Meloxicam was able to diminish the observed increase in spleen weight and reduce elevated ESR dose dependently. Piroxicam was only effective at higher doses, with both diclofenac and tenidap showing no activity at doses sufficient to reduce swelling [34]. Consequently, only meloxicam, at low doses, was able to antagonize immunologically mediated effects.

Meloxicam shows anti-exudative effects which are characteristic of all cyclooxygenase inhibitors tested in rat paw oedema models. Meloxicam displays anti-exudative activity in carrageenan-induced oedema with a potency, at a single oral dose of 1 mg/kg, exceeding that of piroxicam, indomethacin, diclofenac, naproxen and acetylsalicylic acid (Table V). In addition, meloxicam has dose-dependent effects against kaolin-induced oedema which are of a similar potency to piroxicam,

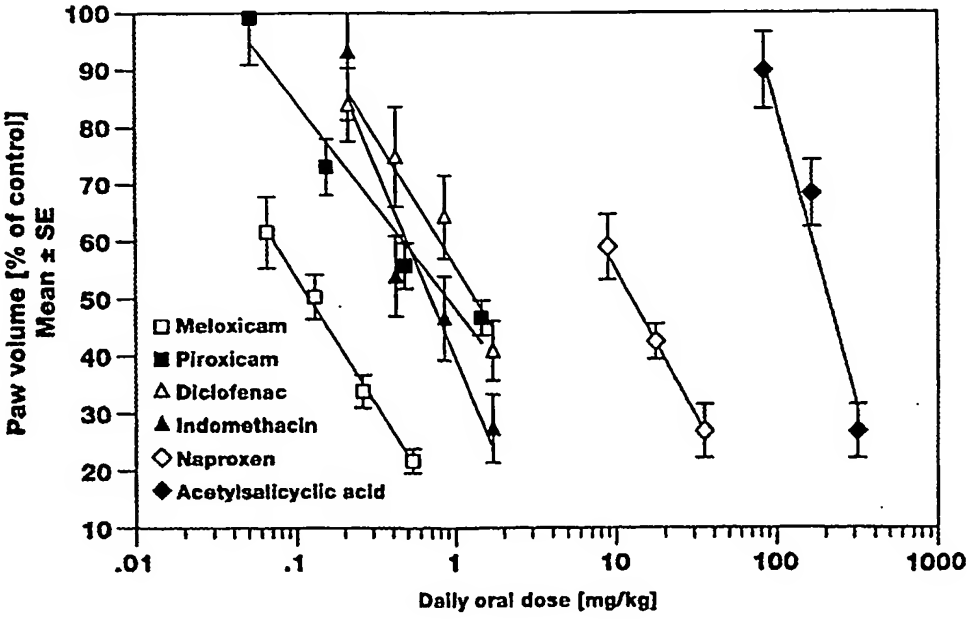

FIG. 3.—Inhibition of adjuvant-induced specific secondary reaction (oedema of the contralateral hind paw) in the rat after daily oral administration for 21 days.

indomethacin and diclofenac and higher than those of tenoxicam, tenidap and naproxen (Table VI). Meloxicam's anti-inflammatory activity is still apparent in adrenalectomized rats, thus indicating that this effect is not mediated by endogenous corticosteroids. However, meloxicam, like other NSAIDs, has no effect on egg white-induced oedema which is mediated by histamine [33].

In another inflammatory model of carrageenan-induced pleurisy of the rat, meloxicam was able to inhibit both exudate formation and polymorphonuclear leucocyte immigration, once again in a dose-dependent fashion. Piroxicam only showed similar effects at doses which were four times greater than equivalent doses of meloxicam [34].

Analgesic effects

Meloxicam, in accordance with findings for diclofenac, indomethacin, piroxicam and naproxen, has no effect on either heat-induced (the hot-plate technique) [35] or mechanically-induced (the tail clamp test) [36] pain in the mouse or on the visceral pain reflex in the rat [37]. Therefore, it can be assumed that meloxicam has no central analgesic effects [33].

Against inflammatory pain, measured according to Randall and Selitto [38] in the rat, meloxicam showed a very prolonged effect. Following a single oral administration the analgesic effect of meloxicam is not reduced by 50% until 18 hours after administration. Meloxicam has a markedly longer duration of action than piroxicam, diclofenac and indomethacin.

Antipyretic effects

Unlike paracetamol and phenazone derivatives, meloxicam and all other NSAIDs have no influence on the body temperature of a normothermic mammal, because NSAIDs have no direct effect on the calorific centre. NSAIDs are only effective against pyrogen-induced fever. Meloxicam shows a lower potency against yeast-induced pyrexia than diclofenac and piroxicam [33]. At a dose of 0.1 mg/kg meloxicam reduces endotoxin-induced fever in the cat [39].

Gastric tolerance

It is widely accepted that gastric ulcerogenicity is the dose-limiting side-effect common to all established NSAIDs. Therefore, the ability to achieve a good therapeutic response is determined by the difference between the dose required to obtain the desired effects and the ulcerogenic dose. For currently established NSAIDs this therapeutic margin is quite narrow such that anti-inflammatory potency does not strictly correlate with gastrointestinal tolerance. For example, at therapeutic doses, indomethacin and piroxicam are associated with a higher risk of gastrointestinal toxicity than other NSAIDs [3, 40, 41].

It is apparent that the complex pathogenesis of stomach ulcerations accompanying NSAID therapy is directly related to the inhibition of the biosynthesis of cytoprotective prostaglandins in the gastric mucosa. Specifically, PGE_2 and PGI_2 protect the mucous membrane and inhibit acid secretion in the stomach.

As we have seen, meloxicam is a weak inhibitor of PGE_2 production in the rat stomach (Table III). Furthermore, meloxicam is a much less potent stimulant of acid secretion in the rat stomach than, for example, piroxicam and indomethacin [42].

Meloxicam shows weak gastric ulcerogenicity in the rat stomach, in contrast to its potent anti-inflammatory efficacy (Table IV). These characteristics are particularly striking when viewed in the context of ratios obtained for other NSAIDs in the same model. Specifically, the therapeutic range displayed by meloxicam in the rat is 10–90 times greater than that of other commonly used NSAIDs [24].

Thus, it is tempting to suggest that based on the unusual parity of meloxicam's pharmacokinetic data in rat and man, that pharmacodynamic and toxicological similarities may also exist [43]. However, such judgements can only be made following the results of clinical investigation.

Effects on renal function

In a standard model used to assess the effect of NSAIDs on renal function, meloxicam, at doses of up to 16 mg/kg, has no influence on water and electrolyte excretion. In contrast, phenylbutazone displays a potent inhibitory effect in the same model using water and electrolyte-loaded rats [44].

Effects on cartilage metabolism

It has been suggested that treatment with NSAIDs can contribute to cartilage deterioration [45], but there is no evidence that meloxicam causes this problem. In long-term studies in rats and mice meloxicam has been

TABLE V

Inhibition of carrageenan-induced oedema in the rat hind paw: measurement of the effect of single oral doses by AUC

NSAID	AUC (% inhibition × h)/mg/kg
Meloxicam	254
Piroxicam	144
Indomethacin	84
Diclofenac	59
Naproxen	44
Acetylsalicylic acid	1.6

TABLE VI

Inhibition of hind paw oedema of rats induced by kaolin 5.5 h after oral administration

Drug	ID_{35} (mg/kg)	Confidence limits (95%)	Regression coefficient
Meloxicam	3.35	2.93–3.91	34.5
Piroxicam	2.71	2.30–3.25	30.8
Tenoxicam	8.35	6.87–10.7	29.0
Tenidap	6.06	4.37–13.1	44.5
Indomethacin	3.42	2.39–4.49	31.4
Diclofenac	4.03	3.01–5.08	20.8
Naproxen	6.25	5.46–7.11	34.1
Acetylsalicylic acid	318	251–542	29.5

TABLE VII
Mean pharmacokinetic parameters of meloxicam in rat and man

Species	Dose (mg/kg/day)	$C_{max,ss}$ (mg/ml) MV ± S.D.	Cl (ml/min/kg) MV ± S.D.	$t_{1/2}$ (h) MV ± S.D.	Plasma-protein binding (%)	Ref.
Rat*	11 × 1.0	6.3 ± 0.76	0.11 ± 0.04	15.5 ± 6.2	99.5–99.7	[43]
Man	7 × 0.11	0.88 ± 0.20	0.11 ± 0.03	20.4 ± 6.4	99.5–99.7	[57]

*Male rat.

established as chondroneutral towards arthrotic erosions [46]. Meloxicam neither increased nor inhibited the development of spontaneously occurring osteoarthrotic changes in rats and mice. These findings correlate with the results of *in vitro* studies [47, 48] which showed that meloxicam, in contrast to indomethacin and acetylsalicylic acid, does not influence the synthesis and degradation of proteoglycans by human chondrocytes.

Uricosuric effects

Many NSAIDs are able to increase uric acid excretion independently of their anti-inflammatory activity [49]. This uricosuric effect has been demonstrated by piroxicam in patients [50, 51]. In rats, where the uric acid level had been raised through treatment with oxonic acid, meloxicam showed a weaker uricosuric effect than piroxicam [33].

Influence on bronchial muscle

NSAIDs are effective inhibitors of bradykinin-induced bronchospasm in guinea-pigs [52]. The bronchospastic effect of bradykinin is an indirect effect, mediated by TXA_2 liberated in the lung [53]. After intraduodenal administration, doses of meloxicam which were effective against bradykinin-induced bronchospasm in guinea-pigs were in the same range as those shown by indomethacin [33].

Unlike piroxicam and diclofenac, even at very low intravenous doses, meloxicam had an effect on PAF-induced bronchospasm in the guinea-pig. PAF-induced bronchospasm is mediated by TXA_2 [54] and LTC4 [55].

Even at high doses, meloxicam has no broncholytic or bronchoconstrictive effect on acetylcholine-induced bronchospasm in the guinea-pig [33].

General pharmacology

A number of studies have been carried out in mice to examine the effect of meloxicam on CNS functions. Oral doses of meloxicam of up to 25 mg/kg did not affect reflexes or sensory functions and had no effect on spontaneous motility; nor did it affect hexobarbital-induced sleeping time. No muscle-relaxant activity was seen at pharmacologically relevant doses. Meloxicam also has no anticonvulsant properties. It did not affect pentetrazole-induced shock or maximal electric shock at doses up to 50 mg/kg, nor did it enhance or reduce the anticonvulsant effect of phenobarbitone on mice subjected to electric shock [44].

Meloxicam has been tested for possible cardiovascular side-effects in a number of species [42]. Even at high oral doses, meloxicam had no significant effect on systolic pressure of the conscious rat. When administered intraduodenally to anaesthetized cats, very high dose levels of meloxicam (100 and 200 mg/kg) caused a slight, but not significant, reduction in mean blood pressure together with a slight decrease in heart rate. Even after high doses, meloxicam had no effect on respiratory minute volume. When administered intravenously to anaesthetized cats, meloxicam had no effect on systolic pressure, diastolic pressure, carotid artery flow, heart rate, electrocardiogram or respiratory volume at doses of up to 4 mg/kg. Oral doses of 2–8 mg/kg had no effect on mean arterial pressure in conscious dogs [56].

In conscious rats, oral doses of meloxicam up to 32 mg/kg had no significant effect on intestinal transit time [44]. Meloxicam remains free of any effect on stomach emptying in conscious rats at doses up to an oral dose of 32 mg/kg [44].

Meloxicam does not affect carbohydrate metabolism. There were no changes in blood glucose levels in rabbits when meloxicam was administered orally at doses up to 4 mg/kg [56].

Meloxicam had no influence on thromboplastin time in the rat when given orally at doses up to 8 mg/kg, on two consecutive days [56].

In *in vitro* studies carried out on isolated organs of guinea-pigs and rats, meloxicam was found to have no anticholinergic, papaverine-like, H_1-antagonist, angiotensin II-antagonist, PGE_2-antagonist, serotonin-antagonist or bradykinin-antagonist properties at concentrations up to 10 µg/ml in a protein-free medium [53].

In summary, the general pharmacology studies did not reveal any pharmacodynamic effects of meloxicam which would restrict its therapeutic use as an NSAID.

Pharmacodynamic interactions

The pharmacokinetic profile of meloxicam in the rat (especially in male rats, commonly used in pharmacological tests) is very similar to its pharmacokinetic profile in man (Table VII) [43, 57]. Consequently, most of the studies designed to detect interactions between meloxicam and other drugs have been carried out in the rat.

Concomitant administration with paracetamol enhances the effect of meloxicam on inflammatory pain in the rat. The doses of paracetamol used had only very weak analgesic activity [56].

Similarly, paracetamol enhances the acute anti-exudative effect of meloxicam in carrageenan-induced paw oedema in the rat [56].

Concomitant administration of pirenzepine with meloxicam minimizes the ulcerogenic effect of meloxicam in the stomach of the rat in a dose-dependent manner [56].

Meloxicam does not reduce the increase in water and electrolyte excretion which is seen in rats after administration of chlortalidone [56].

At very high doses (4 mg/kg and above), meloxicam augments the increase in prothrombin time which is caused by phenprocoumon in the rat [56].

Meloxicam does not influence the effect of tolbutamide on blood glucose levels in the rabbit [56].

Pharmacodynamic effects of metabolites of meloxicam

Four principal metabolites of meloxicam have been identified in rats and humans. These metabolites are rapidly excreted in the urine and are, therefore, not detectable in the plasma [58].

The metabolites did not show any inhibitory effects on COX or display any anti-inflammatory or analgesic activities in the rat following oral administration [59]. Doses up to 10 times higher than active doses of meloxicam were administered in these studies.

CONCLUSIONS

Using models of chronic inflammation in conjunction with a model of gastric damage, meloxicam has been identified as a NSAID with greater anti-inflammatory activity than existing drugs and low toxicity in the stomach. The compound has now been shown to be a preferential inhibitor of COX-2.

This review has focused on presenting the pharmacodynamic activity of meloxicam and has concentrated on its effects on the classical mediators of inflammation which are the common site of action for all NSAIDs. Furthermore, meloxicam's action has been compared with that of well established conventional NSAIDs. This has enabled us to show a clear differentiation between meloxicam's anti-inflammatory profile and that of other NSAIDs in current clinical use. These effects have been demonstrated in a variety of cell types and tissues.

The basis of meloxicam's superior risk–benefit profile over existing NSAIDs (e.g. piroxicam, diclofenac, naproxen, flurbiprofen) can be explained by its selective inhibition of COX-2 in preference to COX-1. However, there are other differences in the pharmacodynamic profile of meloxicam in comparison with other NSAIDs. Anti-inflammatory doses of meloxicam do not influence lipoxygenase activity. Meloxicam does not increase LTC4 content of tissue and has no influence on bronchial tone. That means that the risk of bronchoconstriction may be lower with meloxicam than with known NSAIDs.

Like other NSAIDs, meloxicam displays classical anti-inflammatory, antipyretic and analgesic properties. However, in the model of an acute oedema in the rat, meloxicam has a stronger and much more sustained anti-inflammatory effect than piroxicam, diclofenac and indomethacin. More importantly, meloxicam has a much greater potency in the rat model of progressive and destructive joint disease, adjuvant arthritis, preventing not only oedema but also bone and cartilage destruction. Meloxicam's superior antiarthritic activity may be due to both its high potency against COX-2 [18] and its accumulation in inflamed tissue [60].

In contrast to conventional NSAIDs, anti-inflammatory doses of meloxicam inhibit leucocyte migration. Like other NSAIDs, meloxicam does not show true central analgesic effects. However, this is not relevant with regard to its effect on inflammatory pain.

Meloxicam has no direct influence on the caloric centre and only weak effects against pyrogen fever. It has a mild uricosuric effect. Thus meloxicam is not an alternative to conventional antipyretic or uricosuric drugs.

Meloxicam, in contrast to indomethacin and acetylsalicylic acid, is chondroneutral.

As meloxicam does not affect water and electrolyte excretion and has only a weak influence on intrarenal PGE_2 biosynthesis, it would not be expected to influence kidney function at therapeutic doses. The ulcerogenic potency of meloxicam on the stomach in relation to the anti-inflammatory potency is weak. Pharmacological and toxicological findings suggest that meloxicam is not associated with any side-effect unrelated to its mechanism of cyclooxygenase inhibition. Only the native compound has a pharmacodynamic activity; the metabolites of meloxicam are inert.

The pharmacokinetic behaviour of meloxicam in the rat [43] is very similar to that observed in man [61]. Therefore, pharmacodynamic and toxicological findings with meloxicam established in the rat [37] can be extrapolated, with confidence, to man.

In clinical study, analysis of the safety data from over 4000 patients suggests that meloxicam is fulfilling its early promise from pre-clinical studies [62]. In particular, analysis of upper GI perforations, ulcerations and bleeding indicates a much lower likelihood of occurence in those patients treated with meloxicam 7.5 mg and 15 mg once daily than with therapeutically equivalent doses of piroxicam, diclofenac and naproxen.

For the new compounds described to be selective COX-2 inhibitors (DUP-697 [63], SC-58125 [64], NS-398 [65], L-745,337 [66]) unfortunately clinical data are not available. An improved gastric tolerance of flosulide has been confirmed in humans [67]. The claimed selectivity of nimesulide for COX-2 [68] is not proved by the cited [69] data.

In summary, in this review we show that meloxicam is a NSAID which has the potential to redefine our expectations of risk–benefit ratio associated with current NSAID treatment of inflammatory disease. The explanation of the exceptional pharmacological profile of such an agent has been enabled through new insights into the mode of action of NSAIDs.

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SAFETY OF MELOXICAM: A GLOBAL ANALYSIS OF CLINICAL TRIALS

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SUMMARY

Meloxicam is a new preferential cyclooxygenase-2 (COX-2) inhibitor for the treatment of rheumatic disease. This paper presents a global safety analysis of data from meloxicam clinical studies, focusing on gastrointestinal (GI) adverse events. Meloxicam 7.5 and 15 mg (n = 893 and 3282) were compared with piroxicam 20 mg (n = 906), diclofenac 100 mg slow release (n = 324) and naproxen 750–1000 mg (n = 243). With respect to all GI adverse events, meloxicam 7.5 and 15 mg were significantly better than all comparators in a pooled analysis of double-blind studies in rheumatoid arthritis (RA) and osteoarthritis (OA). When examining non-serious GI events, severe GI events, discontinuations due to GI events, dyspepsia, abdominal pain and upper GI events, both meloxicam doses were significantly better than comparator non-steroidal anti-inflammatory drugs (NSAIDs) in most cases. Where statistical significance was not demonstrated, there was generally a trend in favour of meloxicam. With respect to upper GI perforations, ulcerations and bleedings, the most serious of NSAID-associated side-effects, meloxicam was better tolerated than the comparators, reaching statistical significance for piroxicam and naproxen. Meloxicam's improved GI safety profile is likely to be due to its preferential inhibition of inducible COX-2 relative to constitutive COX-1.

KEY WORDS: Meloxicam, NSAID, Safety, Gastrointestinal, PUB, Cyclooxygenase.

NON-STEROIDAL anti-inflammatory drugs (NSAIDs) are the most common pharmacological treatment for rheumatic disease; their use, however, is limited by the associated high incidence of side-effects, particularly in the gastrointestinal (GI) tract. Although serious events such as perforation, ulceration and bleeding are associated with NSAID use, the most common side-effects are less serious, with symptoms being described as dyspeptic in about half of affected patients [1]. However, serious events are a considerable problem, as the estimated incidence of NSAID-related GI hospitalizations in arthritis patients is between 0.4 and 1.3% per year [2]. Large case-control studies have examined the risk of GI perforation and bleeding with different NSAIDs and in different patient groups [3, 4]. The studies showed that there are differences in GI toxicity between NSAIDs, and the risk increases with higher doses. The risk is greatest in the elderly, patients with a previous history of such events and those treated with concomitant corticosteroids [4, 5].

It is well established that the inhibition of prostaglandin (PG) synthesis, mediated by the cyclooxygenase (COX) enzyme, is responsible for both the anti-inflammatory actions and ulcerogenic potential of NSAIDs [6]. However, it has not been clear why there are differences between agents in terms of their potential to cause GI side-effects, while displaying similar anti-inflammatory potency. The discovery of two isoforms of the COX enzyme, COX-1 and COX-2 [7], has gone some way towards explaining this [8]. Recent findings have suggested that the anti-inflammatory actions of NSAIDs are primarily mediated through the inhibition of the inducible enzyme COX-2, whereas unwanted adverse effects, such as gastric and renal toxicity, are due to inhibition of the constitutive enzyme, COX-1 [8]. COX-1 activity is thought to be necessary to protect the stomach, kidney and possibly other organs against damage. It has been suggested that future advances in NSAID therapy could be achieved via preferential COX-2 inhibition, thus maintaining cytoprotective PG biosynthesis, and avoiding the adverse effects which characterize conventional NSAID therapy [8].

Meloxicam is a new NSAID which preferentially inhibits COX-2 relative to COX-1, as consistently demonstrated in a number of models [9–11]. In animal studies, this mode of action appears to be reflected in a favourable GI tolerability profile [12]. It is important to establish whether this is also indicated in clinical data from studies comparing meloxicam with equipotent doses of standard NSAID therapies.

This overview presents the safety results from a multinational meloxicam clinical study programme conducted in rheumatoid arthritis (RA), osteoarthritis (OA) and other rheumatic diseases. Meloxicam doses used in the clinical trial programme ranged from 7.5 to 60 mg daily. Meloxicam 30 and 60 mg did not show advantages in their benefit/risk ratios compared with standard NSAIDs and, consequently, further investigation of these doses was discontinued. Data from patients treated with meloxicam 7.5 and 15 mg once daily are reviewed. The safety analysis will focus mainly on GI side-effects, as these are of special interest with respect to the tolerability of NSAIDs.

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TABLE I
Overview of studies

	Meloxicam 7.5 mg	Meloxicam 15 mg	Piroxicam 20 mg	Diclofenac 100 mg SR	Naproxen 750–1000 mg
Patient totals	893	3282	906	324	243
Phase I	12	156	0	0	0
Open-label/single-blind	0	1226	174	0	0
Double-blind	881	1900	732	324	243
Mean duration of exposure (days)	70	128	67	92	117
Exposure					
0–≤30 days	567	1646	478	63	41
1–≤6 months	194	886	372	237	115
6 months–≤1 yr	132	320	55	24	87
>1 yr	0	428	0	0	0
Missing values*	0	2	1	0	0

*Patients where the exact duration of treatment is unknown.

TABLE II
Patient characteristics

	Meloxicam 7.5 mg	Meloxicam 15 mg	Piroxicam 20 mg	Diclofenac 100 mg SR	Naproxen 750–1000 mg
Age (mean yr)	59	57	59	66	56
≤65 yr	594	2202	612	145	178
>65 yr	299	1080	294	179	65
Males	265	1176	283	102	71
Females	628	2106	623	222	172
RA	572	1317	381	0	243
OA	309	1511	482	324	0
Other indications*	0	298	43	0	0

*Other indications include sciatica, low back pain and ankylosing spondylitis.

PATIENTS AND METHODS

Clinical studies with meloxicam 7.5 and 15 mg once daily have been conducted in healthy volunteers, and in patients with RA, OA and other rheumatoid diseases. In order to make an overall assessment of the safety of meloxicam, data from individual clinical studies have been pooled. Thus adverse-event data from the clinical trials programme of phase I studies (assessing pharmacokinetics, pharmacodynamics and drug interactions) and phase II/III clinical trials conducted in patients with RA, OA and other indications (including low back pain, sciatica and ankylosing spondylitis) have been analysed. Table I gives the number of subjects who received meloxicam 7.5 or 15 mg or the active comparators, piroxicam 20 mg, diclofenac 100 mg slow release and naproxen 750–1000 mg; the duration of patient exposure to the study drugs and the type of study are also shown. Table II details patient characteristics and disease suffered. For the purposes of the analysis, data from patients receiving naproxen 750–1000 mg were combined. Comparator agents were chosen to reflect current practice in the treatment of arthritic disease with NSAIDs and were considered to be of equivalent therapeutic potency to meloxicam 7.5 and 15 mg.

In phase I studies 168 healthy volunteers received single or multiple oral, rectal, intravenous or intramuscular formulations of meloxicam 7.5 or 15 mg. The clinical trials programme included 34 phase II/III studies in 4007 patients. Early dose-ranging studies conducted in patients with various rheumatoid diseases were open-label, non-controlled pilot studies. The safety and efficacy of meloxicam 7.5 and 15 mg oral formulations (tablets or capsules) were evaluated in seven clinical trials in 1820 patients with OA and in six studies in 1889 patients with RA. The safety data from the double-blind active comparators used in these studies are included in this overall safety analysis.

The majority of oral formulation studies were conducted with meloxicam capsules ($n = 3611$) and the remainder using bioequivalent meloxicam tablets ($n = 188$). Other formulations used included bioequivalent suppositories (one study in OA, $n = 258$) and intramuscular injection (one study in OA and RA and another in sciatica, $n = 209$). Formulations of active comparators used included capsules and ampoules for piroxicam, tablets for naproxen and slow-release tablets for diclofenac.

In RA and OA studies, male and female patients, aged at least 18 yr, were recruited. For OA studies, patients required a clinical diagnosis of OA of the hip or knee, with appropriate radiographic assessments, a defined degree of pain at baseline and treatment with an anti-inflammatory agent had to be considered

beneficial. In RA studies, patients with active RA and a diagnosis of definite or classical RA [13] or with a diagnosis of RA according to the revised criteria of the American Rheumatism Association [14] were included. Second-line therapy was allowed when doses were stabilized before and during the studies. In most studies, stable doses of corticosteroids (up to 7.5 mg prednisone/equivalent/day) were permitted. Paracetamol (up to 4 g/day) was the only permitted rescue analgesic.

Exclusion criteria for RA and/or OA studies included: pregnant or breastfeeding women and women with no adequate contraception; any evidence of severe hepatic, renal, cardiac, metabolic or haematological disease; patients with untreated hypertension; any evidence of concomitant disease which may lead to early termination of the study; patients on prophylactic therapy for bronchial asthma; any evidence of peptic ulceration either current or during the previous 6 months; known hypersensitivity to analgesics, antipyretics and NSAIDs; clinically abnormal laboratory investigations; treatment with any of the following either during or within 3 months of the study: oral corticosteroids (only in OA studies); treatment with intra-articular corticosteroids (a limited number of injections was allowable in RA studies); treatment with other NSAIDs or topical anti-inflammatory preparations, more than 4 g paracetamol/day; prophylactic treatment with any anti-ulcer drugs (however, patients with a history of peptic ulceration could be treated with anti-ulcer drugs) except if necessary for gastroduodenal adverse events occurring during the study; any patient undergoing orthopaedic surgery; removal of fluid from an effusion of the affected joint up to 1 month prior to or during the study; any other rheumatological diseases or non-rheumatological diseases which may interfere with evaluation of safety or efficacy; treatment with any investigational drug within the previous 4 weeks or participation in more than one meloxicam study.

An adverse event was defined as any reaction, side-effect, intercurrent disease or untoward event that occurred during the course of the clinical trial, whether or not the event was considered drug related. Any adverse event that was immediately life threatening, severely or permanently disabling or required, or prolonged, hospitalization was considered to be a serious adverse event. In addition, an adverse event with one of the following outcomes was always considered serious: death, congenital anomaly, cancer or overdose. A severe adverse event was defined as incapacitating, with the inability to do work or usual activity or causing the patient to discontinue from the trial. Coding of adverse events was conducted according to the Adverse Reaction Terminology List (ARTL) of the World Health Organization [15]. In addition to grouping according to the 30-system organ classes, adverse events were also grouped by preferred terms. Preferred terms were counted only once per patient independent of the frequency of their occurrence in this patient and of the number of different terms which were coded under the same preferred term. An adverse event was defined as a PUB (upper GI perforation, ulceration or bleeding) if it was coded as one of the following preferred terms: duodenal ulcer, duodenal ulcer haemorrhagic, duodenal ulcer perforated, duodenal ulcer reactive, gastric ulcer, gastric ulcer haemorrhagic, gastric ulcer perforated, peptic ulcer aggravated, haematemesis or melaena. The classification of PUB included both serious and non-serious adverse events. Adverse events which were recorded during follow-up visits, during prestudy visits and during wash-out periods are not included in the safety analysis.

Statistical analysis

Adverse-event data have been stratified by trial indication (OA or RA), age (<65 yr, ≥65 yr) and meloxicam dose. The Kaplan–Meier estimator [16] was used to calculate the likelihood of a patient remaining free of an adverse event when treated with meloxicam relative to active comparators. This analysis was used to correct for variations in treatment duration occurring between treatment groups. From this analysis the survival curves were drawn for GI adverse events, allowing a visual assessment of the proportion of patients remaining free of an adverse event with meloxicam or comparator drugs over time.

Log-rank tests were conducted between treatment groups on the incidence of adverse events [16]. *P*-values of <0.05 were considered statistically significant.

RESULTS

In total, adverse events from 6129 subjects were included in the pooled safety database, 4175 received meloxicam 7.5 or 15 mg once daily and 1473 received comparator drugs. Table I shows the distribution of patients receiving each treatment and dose of meloxicam. The total exposure to meloxicam was 1475 patient yr, with 428 patients having been treated for a year or more. Exposure by dose is given in Table I.

Table II shows the distribution of patients according to age, sex and indication. The higher mean age of the diclofenac-treated patients resulted from the fact that diclofenac was only used in OA patients who are, on average, older than RA patients.

Gastrointestinal adverse events

The most commonly occurring adverse events involved the GI tract, and these adverse events have, therefore, been analysed most extensively. Data for total GI adverse events are for the whole population and data from subcategories of GI adverse events are presented from double-blind studies in RA and OA only. Data from this subpopulation of patients are presented because data from double-blind studies are clearly the best controlled and most reliable.

In both the whole population and double-blind studies in RA and OA, total (serious and non-serious) GI adverse events occurred most frequently with naproxen 750–1000 mg, followed by diclofenac 100 mg, piroxicam 20 mg, meloxicam 15 mg and meloxicam 7.5 mg (Table III). Both doses of meloxicam were significantly superior to all comparators in double-blind studies in RA and OA ($P < 0.05$, Fig. 1);

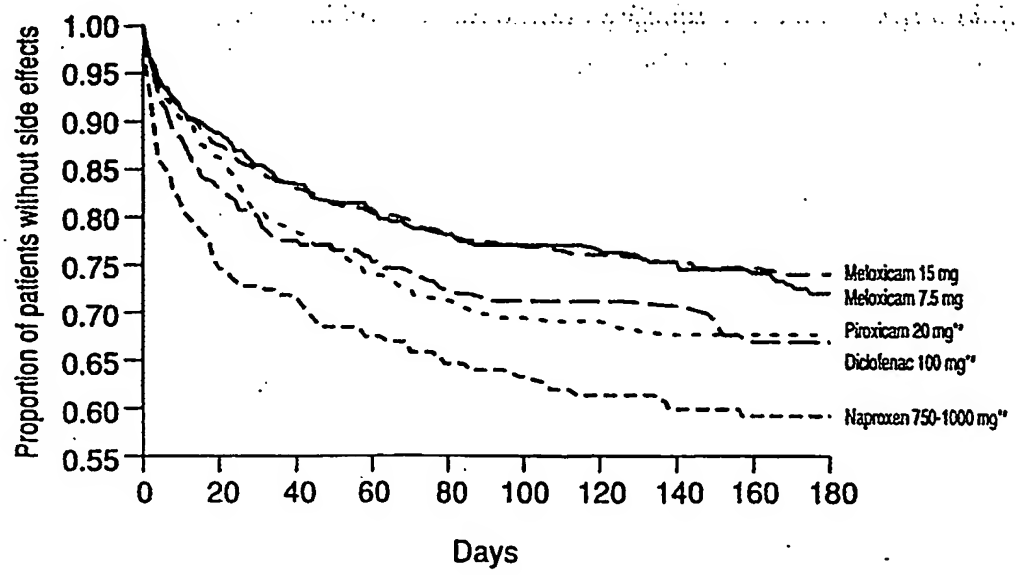

FIG. 1.—Total GI adverse events over time in double-blind clinical studies of meloxicam in RA and OA. $*P < 0.05$ compared with meloxicam 7.5 mg. $\#P < 0.05$ compared with meloxicam 15 mg.

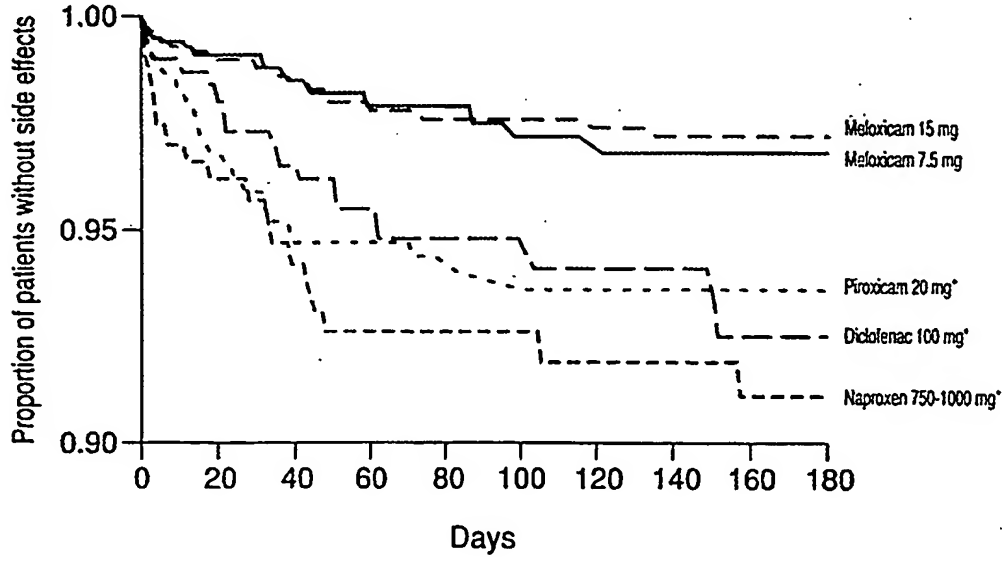

FIG. 2.—Severe GI adverse events over time in double-blind clinical studies of meloxicam in RA and OA. $*P < 0.05$ compared with meloxicam 7.5 mg.

in the whole population, the result was similar with the exception that there was no significant advantage for meloxicam 7.5 mg over piroxicam 20 mg.

The most frequently occurring non-serious GI adverse events (≥2%) in patients treated with meloxicam and active comparators were dyspepsia, nausea, abdominal pain and diarrhoea. There was a similar pattern of frequency with non-serious GI adverse events as with total GI adverse events (Table III). Again, both doses of meloxicam were significantly superior to all comparators in double-blind studies in RA and OA ($P < 0.05$). For GI adverse events defined as severe in intensity, both meloxicam doses were significantly superior to all comparators ($P < 0.05$, Table III). On examination of the survival curve for this parameter, there is a clear difference between both doses of meloxicam *vs* the comparator NSAIDs (Fig. 2). Discontinuation due to GI adverse events was least common with meloxicam 7.5 mg, followed by meloxicam 15 mg, piroxicam 20 mg, diclofenac 100 mg and naproxen 750–1000 mg, with a significant difference between both doses of meloxicam compared with diclofenac and naproxen and between piroxicam and meloxicam 7.5 mg ($P < 0.05$, Table III, Fig. 3).

TABLE III
Incidence of GI adverse events
(all data are from double-blind studies in RA and OA, with the exception of total GI adverse events the whole population)

Adverse event	Meloxicam 7.5 mg	Meloxicam 15 mg	Piroxicam 20 mg	Diclofenac 100 mg SR	Naproxen 750–1000 mg
Total GI adverse events in the whole population % (*n*)	16.8 (150)	18.3 (601)	20.2 (183)†	26.5 (86)*†	36.6 (89)*†
Total GI adverse events % (*n*)	17.0 (150)	18.9 (301)	24.5 (169)*†	26.5 (86)*†	36.6 (89)*†
Non-serious GI adverse events % (*n*)	16.9 (149)	18.8 (299)	24.1 (166)*†	26.2 (85)*†	36.2 (88)*†
Severe GI adverse events % (*n*)	1.7 (15)	1.7 (27)	4.9 (34)*†	4.9 (16)*†	7.8 (19)*†
Discontinuations due to GI adverse events % (*n*)	3.5 (31)	4.8 (76)	6.7 (46)*	10.5 (34)*†	10.7 (26)*†
Abdominal pain % (*n*)	2.7 (24)	3.0 (47)	5.7 (39)*†	7.1 (23)*†	11.9 (29)*†
Dyspepsia % (*n*)	5.1 (45)	7.4 (117)	9.7 (67)*	9.9 (32)*	14.8 (36)*†
Upper GI adverse events % (*n*)	4.5 (40)	5.7 (91)	5.5 (38)	7.1 (23)*	11.5 (28)*†

n, no. of events; %, incidence in percent of treated patients.
*$P < 0.05$ compared with meloxicam 7.5 mg.
†$P < 0.05$ compared with meloxicam 15 mg.
Non-serious adverse events: events other than immediately life threatening, severely or permanently disabling or requiring prolonged hospitalization.
Severe adverse events: incapacitating, with inability to do work or usual activity or causing the patient to discontinue the trial.
Total no. of patients for double-blind studies in RA and OA is 881 for meloxicam 7.5 mg, 1590 for meloxicam 15 mg, 689 for piroxicam, 324 for diclofenac and 243 for naproxen.

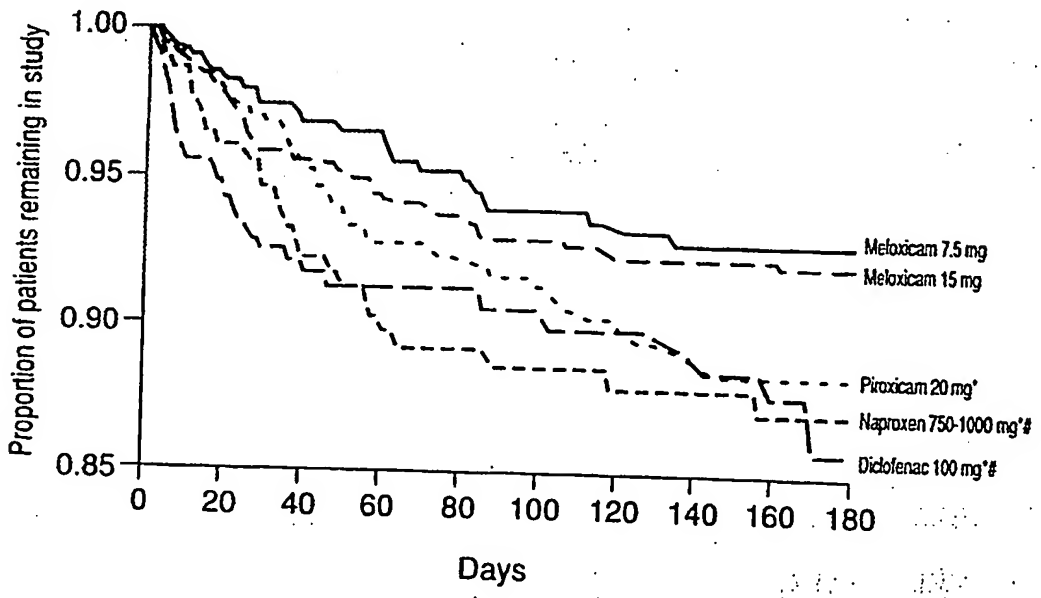

FIG. 3.—Discontinuations due to GI adverse events over time in double-blind clinical studies of meloxicam in RA and OA. *$P < 0.05$ compared with meloxicam 7.5 mg. #$P < 0.05$ compared with meloxicam 15 mg.

When various types of GI adverse events are considered, meloxicam also proved to be better tolerated than the standard NSAIDs. Both meloxicam 7.5 and 15 mg were significantly superior to all comparators with respect to abdominal pain ($P < 0.05$, Table III). For dyspepsia, meloxicam 7.5 mg was the best tolerated, followed by meloxicam 15 mg, piroxicam, diclofenac and naproxen. There were significantly fewer events with meloxicam 7.5 mg compared with piroxicam, diclofenac and naproxen; meloxicam 15 mg

TABLE IV
Type and incidence of PUB in double-blind studies in RA and OA

	Meloxicam 7.5 mg (n = 881)	Meloxicam 15 mg (n = 1590)	Piroxicam 20 mg (n = 689)	Diclofenac 100 mg SR (n = 324)	Naproxen 750–1000 mg (n = 243)
PUB % (n)	0.1 (1)	0.2 (3)	1.2 (8)*†	0.6 (2)	2.1 (5)*†
Serious PUB‡ % (n)	0.0 (0)	0.1 (2)	0.4 (3)	0.6 (2)	0.4 (1)
PUB by age % (n)					
>65 yr	0.0 (0)	0.5 (3)	1.7 (4)*	1.1 (2)	4.6 (3)*
≤65 yr	0.2 (1)	0.0 (0)	0.9 (4)†	0.0 (0)	1.1 (2)†
Type of PUB % (n)					
Duodenal ulcer	0.0 (0)	0.1 (1)	0.6 (4)	0.0 (0)	0.4 (1)
Gastric ulcer	0.1 (1)	0.1 (1)	0.4 (3)	0.3 (1)	1.2 (3)
Melaena or haematemesis	0.0 (0)	0.1 (1)	0.1 (1)	0.3 (1)	0.4 (1)
Perforated upper GI ulcer	0.0 (0)	0.1 (1)	0.1 (1)	0.0 (0)	0.0 (0)
Haemorrhagic upper GI ulcer	0.0 (0)	0.0 (0)	0.1(1)	0.0 (0)	0.0 (0)

n, no. of events; %, incidence in percent of treated patients. Some patients are included in more than one category.
*$P < 0.05$ compared with meloxicam 7.5 mg.
†$P < 0.05$ compared with meloxicam 15 mg.
‡PUBs which were reported as serious adverse events by the investigator (immediately life threatening, severely or permanently disabling or requiring or prolonging hospitalization).

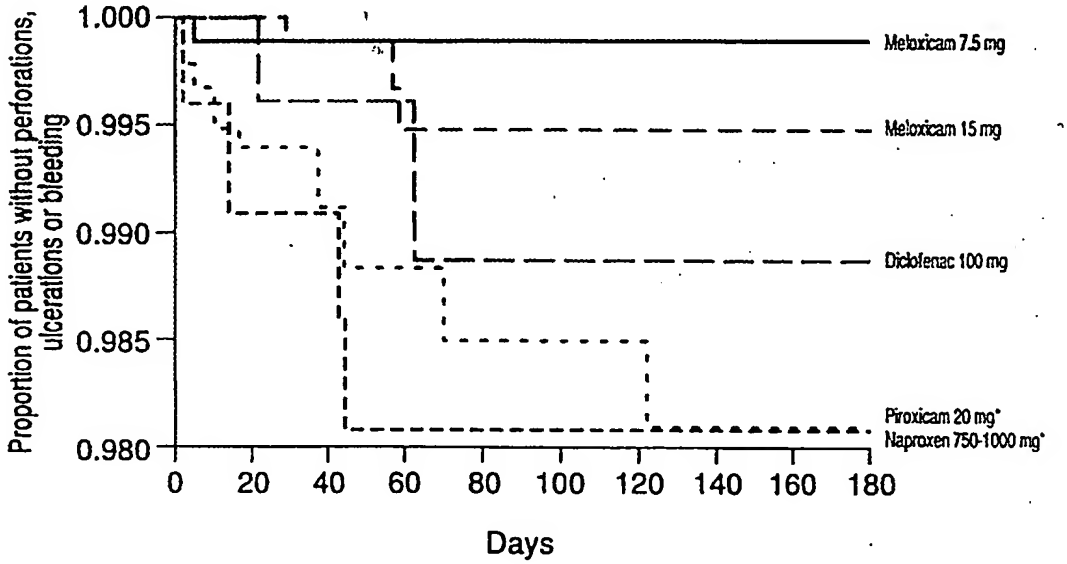

FIG. 4.—Upper GI perforations, ulcerations and bleedings (PUBs) over time in double-blind clinical studies of meloxicam in RA and OA. *$P < 0.05$ compared with meloxicam 7.5 mg.

was significantly superior to naproxen ($P < 0.05$, Table III). With respect to upper GI adverse events (duodenal ulcer, dyspepsia, eructation, nausea, vomiting, gastric ulcer, haematemesis, melaena), meloxicam 7.5 mg was significantly better tolerated than both diclofenac and naproxen; meloxicam 15 mg was significantly superior to naproxen ($P < 0.05$, Table III). These events have also been assessed with respect to their relationship to the drug being studied; similar results were seen when the adverse event was assessed as being at least possibly related to the drug under investigation (results not shown). For abdominal pain, the result in this case was the same as above. For dyspepsia, meloxicam 7.5 mg was significantly superior to both the comparator drugs and meloxicam 15 mg; again, the 15 mg dose was better tolerated than naproxen. For upper GI adverse events at least possibly related to the drug being studied, a greater difference was seen between meloxicam 7.5 mg and the other groups than when all relationships to the drug were considered. For at least possibly related events, there were significantly fewer events with meloxicam 7.5 mg compared with meloxicam 15 mg and piroxicam, in addition to diclofenac and naproxen. Meloxicam 15 mg remained significantly superior to naproxen.

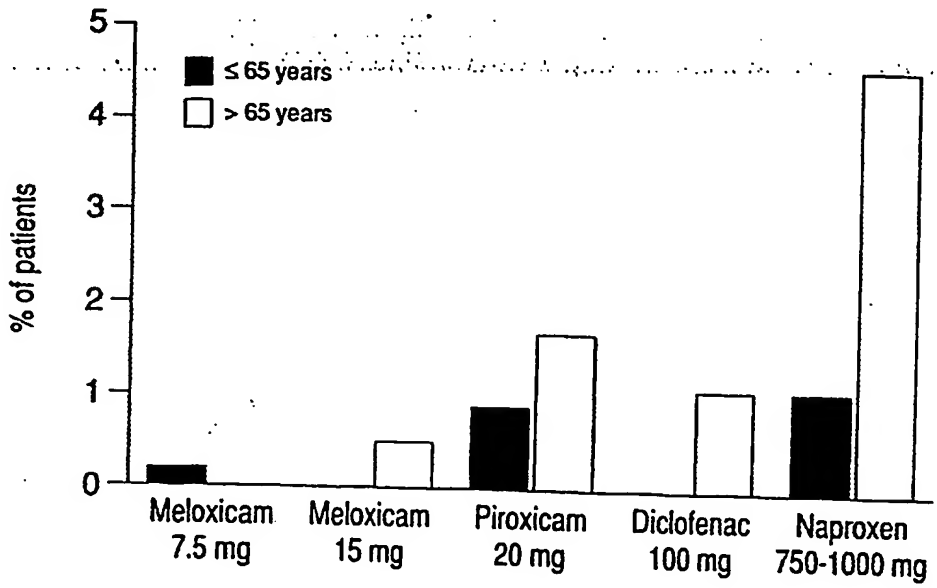

FIG. 5.—Upper GI perforations, ulcerations and bleedings (PUBs) according to age in double-blind clincial studies of meloxicam in RA and OA.

TABLE V
Most frequently occurring adverse events* [*n* (%) of patients treated]

	Meloxicam 7.5 mg	Meloxicam 15 mg	Piroxicam 20 mg	Diclofenac 100 mg SR	Naproxen 750–1000 mg
GI	150 (16.8)	601 (18.3)	183 (20.2)	86 (26.5)	89(36.6)
CNS	69 (7.7)	248 (7.6)	60 (6.6)	22 (6.8)	19 (7.8)
GOT/GPT increased	53 (5.9)	243 (7.4)	57 (6.3)	52 (16.1)	23 (9.5)
Skin and appendages	58 (6.5)	203 (6.2)	40 (4.4)	13 (4.0)	20 (8.2)
Respiratory system	55 (6.2)	239 (7.3)	33 (3.6)	20 (6.2)	15 (6.2)
Urinary system	39 (4.4)	172 (5.3)	44 (4.9)	10 (3.1)	12 (4.9)
Creatinine/BUN increased	4 (0.5)	12 (0.4)	8 (0.9)	1 (0.3)	1 (0.4)

GOT, glutamate oxalate transaminase; GPT, glutamate pyruvate transaminase; BUN, blood urea nitrogen.
*All adverse events, irrespective of causal relationship to study drug, are shown.

Upper GI perforations, ulcerations and bleedings (PUBs) (which includes events defined as serious and non-serious) occurred most frequently in patients treated with naproxen 750–1000 mg, followed by piroxicam 20 mg, diclofenac 100 mg, and meloxicam 7.5 and 15 mg (Table IV, Fig. 4). Although the incidence of PUB was related to meloxicam dose, both meloxicam 7.5 and 15 mg were significantly superior to piroxicam and naproxen ($P < 0.05$). The type and incidence of PUB are summarized in Table IV; gastric and duodenal ulcers were the most common PUBs recorded and were responsible for the higher incidence of PUBs observed with comparator drugs compared with meloxicam.

The percentage of patients with PUBs which were considered serious adverse events was highest in the diclofenac 100 mg group and lowest in the meloxicam 7.5 mg group, where no serious PUBs were reported (Table IV). Meloxicam 7.5 mg was significantly superior to diclofenac ($P < 0.05$) in terms of PUBs considered to be serious. The majority of GI adverse events defined as serious fell into the category of a PUB.

There was a higher incidence of PUB in elderly (>65 yr) than in younger patients (Table IV, Fig. 5). There were fewer PUBs in the meloxicam or diclofenac treatment groups than in the naproxen or piroxicam groups for either elderly or younger patients.

Renal function abnormalities

Sixteen (0.4%) of the 4175 subjects who received meloxicam 7.5 or 15 mg showed significantly abnormal renal function during treatment [defined as serum creatinine > 1.8 mg/dl or blood urea nitrogen (BUN) values >40 mg/dl associated with serum creatinine values above the upper limit of normal, with values recorded during treatment higher than those at baseline]. The percentage of patients with abnormal kidney function values after receiving piroxicam 20 mg was 0.9%, diclofenac 100 mg 0.3%, naproxen 750–1000 mg 0.4% and placebo 0.2%. RA patients are generally known to suffer from a higher rate of renal adverse events with NSAIDs than OA patients, but this was not observed with meloxicam. When RA and OA patients were analysed separately, the same incidence (0.4%) of renal adverse effects was found in both groups. In

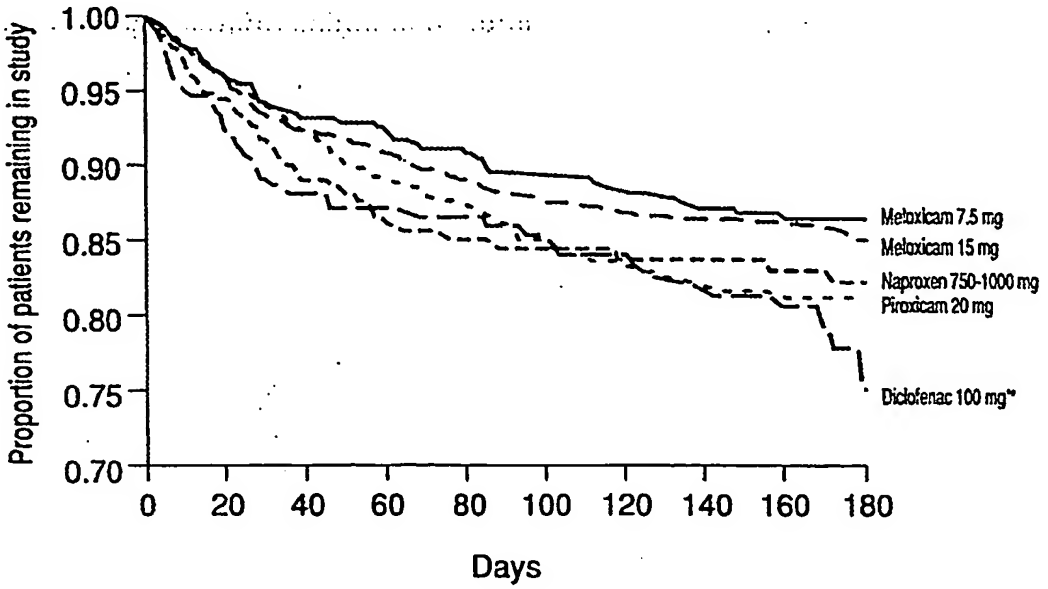

FIG. 6.—Discontinuations due to an adverse event over time in the whole patient population. *#$P < 0.05$ compared with meloxicam 7.5 mg and meloxicam 15 mg.

contrast, piroxicam showed a higher incidence in RA patients (1.6%) compared with OA patients (0.4%).

General analysis of all adverse events (whole population)

There was a trend towards a greater number of adverse events occurring in diclofenac- and naproxen-treated patients than in the other treatment groups. In all groups, the most frequently occurring adverse events were GI events (Table V). Adverse events often associated with NSAIDs were reported with a similar incidence across active treatment groups. These included dizziness, headache, rash, pruritus, hypertension and peripheral oedema.

The incidence of non-serious adverse events recorded was similar between the treatment groups (43%, 45%, 44%, 56% and 61% for meloxicam 7.5 and 15 mg, piroxicam, diclofenac and naproxen respectively). The percentage of patients withdrawn due to an adverse event was lowest in the meloxicam 7.5 mg group, followed by meloxicam 15 mg and piroxicam 20 mg, followed by naproxen 750–1000 mg and diclofenac 100 mg (Fig. 6). Both doses of meloxicam were significantly superior to diclofenac ($P < 0.05$).

One patient who received meloxicam 7.5 mg, five patients who received meloxicam 15 mg and five patients who received comparator drugs died during or after clinical trials (Table VI). In all cases the investigator assessed the relationship of this outcome to the study drug as doubtful.

TABLE VI
Deaths recorded during or after the study period

Treatment group	Reason for death
Meloxicam 7.5 mg	Bronchial neoplasm
Meloxicam 15 mg	Myocardial infarction
	Myocardial infarction
	Septic shock, renal failure*
	Pulmonary carcinoma
	Bronchial carcinoma
Placebo	Sudden cardiac arrest
Piroxicam 20 mg	Rectal carcinoma
	Probable myocardial infarction
Diclofenac 100 mg SR	Pneumonia, spine fracture
Naproxen 750 mg	Adenocarcinoma of the lung

*This patient was a 69 yr old female being treated for RA who received methotrexate as second-line therapy for 4 months. She was hospitalized 17 days following a tooth extraction which led to haematoma of the right jaw. She died in hospital following septic shock which led to heart and renal failure.

DISCUSSION

This first global analysis of safety data from a clinical trial programme for meloxicam, a preferential COX-2 inhibitor, has explored the safety and tolerability of meloxicam in therapeutic doses of 7.5 and 15 mg in 4175 patients, including 1379 patients aged >65 yr, with the majority of patients having OA or RA. This represents a broad database of clinical experience.

The data show that meloxicam 7.5 and 15 mg have a better GI safety profile in comparison with diclofenac 100 mg SR, piroxicam 20 mg and naproxen 750–1000 mg. When considering all GI adverse events, both doses of meloxicam were significantly better than comparators in an analysis of pooled data from double-blind studies in RA and OA. When examining specific categories of GI adverse effects, both doses of meloxicam were significantly better than the comparator NSAIDs in most cases. In the few cases where statistical significance was not demonstrated, there was generally a clear trend in favour of meloxicam.

Dyspepsia, abdominal pain, nausea and diarrhoea were the most commonly occurring adverse events, as is

usual with NSAIDs [1, 17]. Although not life threatening, these symptoms can be extremely unpleasant for the patient and may reduce compliance with therapy. In this analysis, meloxicam showed an advantage with respect to abdominal pain and dyspepsia. As two of the most common NSAID-associated side-effects, abdominal pain and dyspepsia affect large numbers of patients and a good safety profile with respect to these events is essential to patient tolerability, compliance and continued use of therapy. Indeed, discontinuation due to GI adverse events was least common with meloxicam 7.5 mg, followed by meloxicam 15 mg.

Both doses of meloxicam showed a statistically significant decrease in the incidence of PUB over piroxicam 20 mg and naproxen 750–1000 mg; in addition, there was a significant difference in favour of meloxicam 7.5 mg over diclofenac 100 mg with respect to PUBs which were reported as serious adverse events. Diclofenac is thought of as one of the safer NSAIDs with respect to bleeding, perforation and other serious GI adverse events [18]. The risk of PUB is generally greater in the elderly compared with younger patients [4, 19]. With all NSAIDs examined in this analysis, with the exception of meloxicam 7.5 mg, there was a higher incidence of PUB in the elderly than in younger patients. However, the increase in incidence for elderly *vs* younger patients was less for meloxicam 15 mg than for the comparator drugs. No elderly patient (>65 yr) experienced a PUB when treated with meloxicam 7.5 mg.

Although both meloxicam 7.5 and 15 mg showed an advantage over the comparator NSAIDs in their GI safety profile, there was some evidence of a dose–effect relationship with respect to GI side-effects. Overall, meloxicam 7.5 mg was rather better tolerated than meloxicam 15 mg, although there was no statistically significant difference between them with respect to any of the parameters examined. Of the comparator drugs, naproxen 750–1000 mg was the least well tolerated with respect to most categories of GI adverse events. When considering PUBs, diclofenac appeared rather better tolerated than piroxicam, as has been previously observed in epidemiological studies [18]. However, there were fewer non-PUB GI events with piroxicam than with diclofenac. Overall, when considering PUBs and other GI adverse events, meloxicam was consistently the best tolerated of all the drugs compared in this analysis.

Renal impairment is an adverse event also commonly associated with NSAID treatment. This is usually manifested as mild and reversible renal impairment but cases of acute renal failure have also been observed [20]. It is clear that some NSAIDs have a greater likelihood of causing renal impairment than others [21]. In this analysis, treatment with piroxicam 20 mg had the highest risk of inducing an increase in serum creatinine and/or BUN. Meloxicam, naproxen and diclofenac SR treatment groups recorded a similar incidence of renal function abnormalities. The incidence of other adverse events was similar across all treatment groups.

This analysis confirms the now well-recognized fact that there are clear differences between NSAIDs at equipotent doses in terms of their potential to cause GI side-effects [3, 4]. The differential inhibition of COX-1 relative to COX-2 by NSAIDs may explain the differences between them regarding GI tolerability, and presents an opportunity for the development of new NSAID treatment. The favourable GI profile shown by meloxicam compared with piroxicam, diclofenac SR and naproxen in this safety analysis may be a consequence of meloxicam's preferential inhibition of COX-2 over COX-1. In several models designed to investigate the COX selectivity of various NSAIDs, meloxicam has shown preferential selectivity for COX-2 [9–11]. In contrast, NSAIDs such as diclofenac, piroxicam, indomethacin and naproxen either inhibited both COX isoforms to a similar degree or preferentially inhibited COX-1 over COX-2 [9–11, 22, 23]. The relative selectivity of a NSAID is reflected in its COX-2/COX-1 inhibition ratio; low ratios indicate more potent inhibition of COX-2 than of COX-1.

The clinical relevance of differences in COX-2 inhibition relative to COX-1 can be illustrated when NSAID-related upper GI bleeding ratings from case-control studies or UK Committee on Safety of Medicines (CSM) spontaneous adverse event reports are considered [3, 4, 18]. For example, odds ratios for the risk of experiencing an upper GI bleeding and/or perforation from two case-control studies were 18.0 and 13.7 for piroxicam, compared with odds ratios of 3.9 and 4.2 for diclofenac, and 3.1 and 9.1 for naproxen [3, 4]. A similar ranking in the relative incidence of PUBs in CSM spontaneous adverse event reports between these agents was recorded [18]. In this respect, there is a clear link between lower GI toxicity and more potent inhibition of COX-2 relative to COX-1 by these NSAIDs [9, 22]. As meloxicam consistently demonstrates a lower COX-2/COX-1 ratio than these standard NSAIDs, it might be expected that this would be reflected in a superior GI safety profile. The results of the present analysis provide good evidence that this is the case.

In conclusion, it has been shown that meloxicam, at therapeutic doses of 7.5 and 15 mg once daily, has an improved GI safety profile in comparison with standard doses of well-established NSAIDs. This may be explained by meloxicam's preferential inhibition of COX-2 relative to COX-1.

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A SIX-MONTH DOUBLE-BLIND TRIAL TO COMPARE THE EFFICACY AND SAFETY OF MELOXICAM 7.5 mg DAILY AND NAPROXEN 750 mg DAILY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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SUMMARY

Meloxicam is a new non-steroidal anti-inflammatory drug (NSAID) which preferentially inhibits cyclooxygenase-2 over cyclooxygenase-1. A double-blind, parallel-group trial compared meloxicam 7.5 mg once daily ($n = 199$) with naproxen 750 mg ($n = 180$) in rheumatoid arthritis. There was no significant difference between the groups regarding the primary efficacy variables (global efficacy assessment by patient and investigator, number of painful/tender and swollen joints) and eight of the ten secondary efficacy endpoints. Only the swollen joint severity index and the number of discontinuations due to lack of efficacy favoured naproxen 750 mg significantly over meloxicam 7.5 mg. Meloxicam was better tolerated in the gastrointestinal (GI) tract, with fewer GI adverse events in the meloxicam-treated group (30.3%) than in the naproxen-treated group (44.7%), where two patients developed ulcers. No ulcers were seen in meloxicam patients. Significantly more patients discontinued due to GI adverse events in the naproxen group. Additionally, there was a significant decrease in haemoglobin and a significant increase in serum creatinine and urea in the naproxen group compared with the meloxicam group. In conclusion, meloxicam 7.5 mg once daily is a promising treatment in rheumatoid arthritis, with efficacy comparable to naproxen 750 mg. Meloxicam has the advantage of a significantly lower incidence of GI and renal side effects.

KEY WORDS: Meloxicam, Non-steroidal anti-inflammatory drug, Cyclooxygenase-2, Naproxen, Rheumatoid arthritis, Gastrointestinal.

NON-STEROIDAL anti-inflammatory drugs (NSAIDs) are widely used in rheumatoid arthritis (RA) for the relief of pain and inflammation. However, the use of NSAIDs is limited by side-effects, particularly of a gastrointestinal (GI) nature. Vane first recognized that both the anti-inflammatory actions and the common side-effect profile of NSAIDs are mediated through inhibition of prostaglandin biosynthesis via the cyclooxygenase (COX) enzyme [1]. It is now believed that the beneficial effects of NSAIDs are due to the inhibition of one isoform of COX (COX-2, produced by inflammatory mediators), whereas the common side-effects are due to inhibition of COX-1 (which has a 'housekeeping function' in cells) [2]. Compounds that have favourable COX-2/COX-1 ratios should have a less irritant action on the stomach and fewer side-effects [3]. Meloxicam, a new enolic acid NSAID, has demonstrated in preclinical studies to have one of the highest selectivity ratios for COX-2 [4] and has also been shown to have minimal damaging effects on the GI tract [4–7].

In this study, the efficacy and safety of meloxicam 7.5 mg was compared with naproxen 750 mg in patients with RA. Naproxen was chosen for comparison because it is a well established NSAID for use in RA [8–10].

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METHODS

This controlled, double-blind, double-dummy, parallel-group trial was conducted at trial centres located in the UK (23 centres), Germany (13), France (7), Belgium (3), Mexico (1) and Spain (1). The study was approved by the appropriate Ethics Committees and was conducted in accordance with the provisions of the Declaration of Helsinki. All patients gave informed consent to participation in the study.

Patients

Patients, aged 18–75 yr, with RA were enrolled in the study. RA was defined according to the American College of Rheumatology (formerly the American Rheumatism Association) criteria [11] and patients belonged to functional class I, II or III [12], required anti-inflammatory therapy and demonstrated active disease before and/or during a washout period. Active disease was defined as the presence of three of the following: six or more joints painful or tender on motion; three or more swollen joints; duration of morning stiffness of at least 45 min; Westergren sedimentation rate of ≥28 mm/h.

Patients who had taken part in a previous meloxicam trial were excluded, as well as patients with clinical evidence of peptic ulceration and those with any other rheumatological or non-rheumatological disease which would interfere with the evaluation of efficacy and safety, including collagenosis, dermatomyositis, gout,

infectious arthritis, sarcoidosis, psoriatic arthritis, ankylosing spondylitis, Still's disease, mixed connective tissue disease, arthritis associated with inflammatory bowel disease, systemic lupus erythematosus, fibromyalgia, Reiter's syndrome, arteritis (general), polymyalgia rheumatic and scleroderma. Patients were assessed at the start of treatment, at days 14 and 28 and at weeks 8, 12, 19 and 26.

Washout period

After assessment and randomization to meloxicam or naproxen treatment, patients already taking a NSAID underwent a washout period of 3–11 days (dependent upon the drug).

Medication

Following the washout period, the patients were instructed on how to take their trial medication: one capsule (meloxicam 7.5 mg or matching placebo) and two tablets (naproxen 250 mg or matching placebo) each morning and one tablet (naproxen 250 mg or placebo) each evening, all with water after food.

Concomitant medication was allowed but patients whose treatment with second-line antirheumatic therapies was not stable for 3 months before the study were excluded. Those treated with any glucocorticosteroid exceeding a dose of 7.5 mg prednisolone daily (or equivalent) and not stabilized for a month before the study were also excluded. Patients could not receive any intramuscular or intravenous injections of glucocorticosteroids or adrenocorticotrophic hormone and no more than two intra-articular injections of corticosteroids in the month before the study or during the study itself. The doses of second-line therapies and oral corticosteroids could be reduced but not increased. However, following a dose reduction, a subsequent increase to the original dose was permitted. If a patient required an increase in dose beyond the original dose, he or she had to be withdrawn from the study.

No analgesics other than paracetamol were allowed during the trial and it was stressed to patients that this should only be taken when absolutely necessary and the daily dose was not to exceed 4 g. Physiotherapy could be continued throughout the study.

Primary and secondary efficacy endpoints

There were four primary endpoints for the assessment of efficacy. The patient and the investigator assessed global efficacy using horizontal visual analogue scales (VAS). The question asked was: 'How effective has the trial drug been?'. Additionally, at the end of the study or at the withdrawal visit, the following question was asked: 'How effective has the trial drug been throughout the whole trial period?'. The two ends of the 10 cm VAS were defined by vertical lines, with the words 'excellent' on the left and 'useless' on the right. In addition, the number of painful and/or tender joints and the number of swollen joints were determined.

There were nine secondary endpoints for efficacy. Grip strength of the right and left hands was measured using a Martin Vigorimeter®. The swollen joint severity and painful and/or tender joint severity indices were assessed by examination of 68 joints and assigning a score to each on a four-point scale (0 = none, 3 = severe). Pain in the morning and at night was assessed as well as the duration of morning stiffness. The difficulty in performing eight activities of daily living (ADL) was assessed by the patient using a self-report questionnaire. The ADL were: (i) dress yourself, including tying shoe laces and doing buttons; (ii) get in and out of bed; (iii) lift a full cup or glass to your mouth; (iv) walk outdoors on flat ground; (v) wash and dry your entire body; (vi) bend down to pick up clothing from the floor; (vii) turn normal taps on and off; and (viii) get in and out of a car. Additionally, analgesic consumption was assessed by the number of paracetamol tablets taken between visits. The number of patients who reduced oral corticosteroid doses, the time course of global efficacy and the drop-out rate due to lack of efficacy were also considered. Erythrocyte sedimentation rate (ESR) was measured.

Safety endpoints

Endpoints used to consider safety included assessment of global tolerance by the patient and investigator using a VAS (the two ends of the 10 cm VAS were defined by vertical lines with the words 'excellent' on the left and 'extremely bad' on the right), the time course of global tolerance, the number and severity of adverse events and the drop-out rate due to adverse events. The relationship of the trial drug to all adverse events was assessed by the investigator according to the classification of Karch and Lasagna [13]. Haematology, biochemistry and urinalysis laboratory investigations were performed. At the screening visit, the rheumatoid factor was measured.

Statistical methods

Results were reported as exploratory significant if $P < 0.05$. Analyses were undertaken on an intent-to-treat basis (all randomized patients). Baseline characteristics were evaluated using the two-sample *t*-test or the *U*-test. Primary endpoints were analysed by the method of two one-sided *t*-tests. The efficacy parameters and meloxicam plasma concentrations were analysed with the analysis of covariance (ANCOVA) model.

Incidence, time, severity and causal relationship of the adverse events were tabulated by body system organ class and crude as well as hazard rates were estimated. The evaluation of laboratory values was performed by score analysis referring to the normal ranges of the parameters [14]. Furthermore, the values were checked for clinically relevant changes by shift tables.

The null hypothesis of interest was that the magnitude of response with regard to the primary endpoints should be the same in both treatment groups. It was calculated that a sample size of at least 140 evaluable patients per treatment group would be sufficient to detect a difference of 20% or more by means of a two-sample *t*-test ($\alpha = 5\%$, $\beta = 10\%$, two-

tailed). Due to their expected high correlation, no alpha-adjustment for multiple testing was foreseen.

RESULTS

Three hundred and seventy-nine patients were randomized, 199 to treatment with meloxicam and 180 to treatment with naproxen. The data from these patients were included in the intent-to-treat analysis. Efficacy and safety parameters were assessed after 26 weeks of treatment (i.e. at completion) or at the last trial visit (i.e. at early withdrawal due to lack of efficacy, adverse events or other reasons).

The mean duration (± S.D.) of RA at baseline was comparable, with 9.3 ± 10.1 years in the meloxicam group and 9.2 ± 9.9 years in the naproxen group. The patients in the two groups had comparable disease characteristics at baseline (Table I). One hundred and seventy-two (86.4%) of the patients in the meloxicam group and 168 (93.3%) in the naproxen group had been treated previously with NSAIDs. Second-line therapies were used by 127 (63.8%) patients in the meloxicam group and 124 (68.8%) patients in the naproxen group. The second-line drugs used most frequently were sulphasalazine, methotrexate, penicillamine, sodium aurothiomalate and auranofin. Only a small number of patients (<10% in each group) received treatment with steroids.

TABLE I
Disease characteristics at baseline

	No (%) of patients		
	Meloxicam (n = 199)	Naproxen (n = 180)	Missing observations
Morning stiffness of at least 45 min	186 (93.4)	163 (90.5)	0
Soft tissue swelling in ≥3 joints	199 (100)	176 (97.7)	0
Symmetric swelling ≥6 weeks	192 (96.4)	173 (96.1)	0
Rheumatoid nodules	51 (25.6)	59 (32.7)	5
Rheumatoid factor positive*	134 (67.3)	133 (73.8)	0
ESR at least 28 mm/h	124 (62.3)	114 (63.3)	13
Radiographic erosions/ osteopenia in hand/wrist joints	163 (81.9)	141 (78.3)	4
Extra-articular organ involvement of RA	3 (1.5)	2 (1.1)	1
Acute onset of disease	82 (41.2)	86 (47.7)	2
Chronic progressive course of disease	143 (71.8)	127 (70.5)	0

*Presence of rheumatoid factor measured at the pre-study visit.

Primary efficacy variables

On average, the investigators rated global efficacy somewhat better for naproxen than for meloxicam. For patients who completed 6 months of treatment (106 naproxen-treated patients and 117 meloxicam-treated patients), the mean VAS values were 2.8 ± 2.5 and 3.2 ± 2.6 cm for naproxen and meloxicam respectively. At the last trial visit, including patients who withdrew early, the corresponding values were 4.2 ± 3.2 and 4.8 ± 3.3 cm. These differences were not statistically significant.

The patients' assessment of global efficacy was similar to that of the investigators. Global efficacy assessed by the patient at each study visit is shown in Fig. 1. Global efficacy assessment was not influenced by the patients' age, sex, or weight or by the study centre or country. However, patients with a duration of RA of 8 years or less rated final global efficacy better than those with a duration of >8 years. Investigator assessments of global efficacy rated both trial drugs considerably better in patients not receiving concomitant corticosteroids than in those who were receiving concomitant corticosteroids. A similar pattern was observed with concomitant intra-articular therapy.

The mean number of painful/tender joints was reduced in the meloxicam-treated group by 8.01 and 5.51 at 26 weeks and at the last trial visit respectively. The corresponding figures in the naproxen-treated group were 10.95 and 7.45. For swollen joints, the mean number was reduced by 6.13 and 3.56 in the meloxicam group and 7.20 and 5.76 in the naproxen group. For both variables there was a significant improvement versus baseline but the difference between the two treatment groups was not statistically significant.

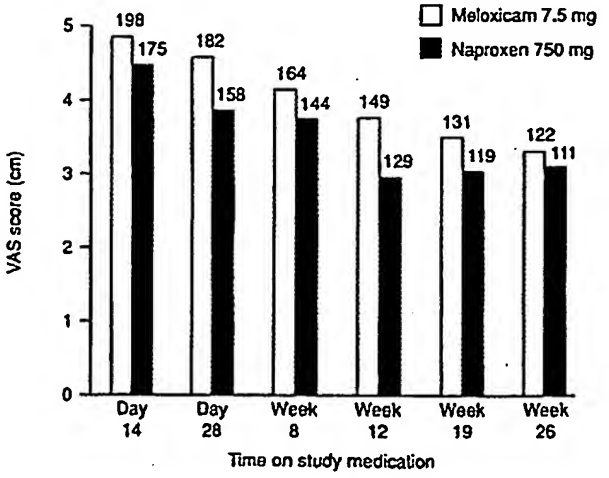

FIG. 1.—Mean global efficacy assessed by patient over the study period. This was measured using a 10 cm VAS scale, where 0 = excellent and 10 = useless. A higher value on the VAS indicates less efficacy. Numbers above the bars indicate the number of patients.

Secondary efficacy variables

Forty-seven patients (23.6%) treated with meloxicam and 26 (14.4%) patients treated with naproxen discontinued the trial prematurely due to lack of efficacy. This difference was statistically significant ($P = 0.036$). There appeared to be no correlation between the rate of discontinuation and any other factor, such as patient characteristics or second-line therapy.

In the meloxicam group all secondary endpoints displayed a statistically significant improvement from baseline to 26 weeks and from baseline to last observation. For the naproxen-treated patients the last value ESR did not display a statistically significant improvement from baseline. Changes from baseline to last observation are shown in Table II. Most variables showed no significant difference between patient groups, either at last observation or at completion of treatment. Naproxen patients showed a mean reduction of 9.43 for swollen joint index; this was superior to the change observed with meloxicam patients, who demonstrated a reduction of 4.19 (at last observation). The difference between the groups was highly significant ($P = 0.01$). The mean paracetamol consumption per month did not differ significantly between the meloxicam-treated group and the naproxen-treated group (50.4 ± 58.1 tablets versus 46.2 ± 58.6 tablets). There was no statistically significant difference between the treatment groups with regard to concomitant corticosteroid therapy.

A possible influence on efficacy caused by changes in concomitant therapy, including the number of intra-articular injections and the dose of oral corticosteroids during the trial, was investigated. Second-line therapy was changed in 5.0 and 8.2% of patients in the meloxicam- and naproxen-treated groups respectively. However, there was no statistical difference with regard to changes in any concomitant therapies between the treatment groups.

Safety

Adverse events. One hundred and twenty-five patients (62.8%) on meloxicam treatment and 106 patients (58.8%) receiving naproxen reported adverse events. Adverse events were considered to be at least probably related to treatment in 8.5 and 13.8% of meloxicam and naproxen patients respectively, and at least possibly related in 34.6 and 39.4% respectively. Twenty-five (12.5%) patients in the meloxicam group and 29 (16.1%) patients in the naproxen group withdrew from the study due to adverse events (Table III).

Gastrointestinal adverse events. The majority of GI adverse events included dyspepsia, diarrhoea, nausea and abdominal pain. A total of 71 GI adverse events occurred in patients treated with meloxicam (0.36 events per patient) compared with 93 events (0.52 events per patient) in naproxen-treated patients. This difference was statistically significant ($P = 0.002$).

The number of patients who experienced GI adverse events was lower in the meloxicam group (53; 26.6%) than in the naproxen group (64; 35.5%). There was a significant difference ($P = 0.046$) between the treatment groups with respect to the number of patients discontinuing due to GI adverse events: 12 (6.0%) and 22 (12.2%) patients in the meloxicam and naproxen groups respectively. No patients in the meloxicam group experienced ulcers and/or perforations or bleeding of the GI tract, whereas two patients in the naproxen group suffered a duodenal ulcer (diagnosed by X-ray) and a peptic ulcer (diagnosed by gastroscopy) respectively.

TABLE II

Secondary efficacy variables: changes of variables from baseline until the last observed value (end of trial or withdrawal visit)

Variable	Meloxicam	Naproxen
Grip strength right (kPa)	3.99 (± 14.57)	3.04 (± 13.44)
Grip strength left (kPa)	4.87 (± 16.40)	3.26 (± 15.57)
Swollen joint severity index	−4.19 (± 18.45)*	−9.43 (± 18.01)*
Painful/tender joint severity index	−9.92 (25.63)	−13.66 (± 23.89)
Morning stiffness (min)	−18.81 (± 89.31)	−23.09 (± 103.6)
Erythrocyte sedimentation rate (mm/h)	−2.33 (± 20.56)	−2.31 (± 19.59)
Activities of daily living difficulties (scores)	−0.06 (± 0.47)	−0.12 (± 0.55)
Pain in morning (VAS, cm)	−1.07 (± 2.98)	−1.50 (± 3.22)
Pain at night (VAS, cm)	−0.57 (± 3.27)	−0.93 (± 2.96)

Values are given as mean (± S.D.).

*Statistically significant difference ($P = 0.01$) between treatment groups.

TABLE III

Number (% of patients treated) of patients who discontinued due to adverse events

WHO system organ class (SOC)	Meloxicam	Naproxen
Skin and appendages	6 (3.0)	2 (1.1)
Central and peripheral nervous systems	0 (0)	1 (0.6)
Gastrointestinal system	12 (6.0)	22 (12.2)*
Liver and biliary system	3 (1.5)	1 (0.6)
Respiratory system	1 (0.5)	0 (0)
White cells and RES	1 (0.5)	0 (0)
Neoplasms	0 (0)	1 (0.6)
Resistance mechanism disorder	2† (1.0)	0 (0)
Discontinuation due to adverse events in several SOC	5 (2.5)	9 (5.0)
Total no. of patients	25 (12.5)	29 (16.1)

Some patients discontinued due to an adverse event in more than one system organ class. RES denotes reticulo-endothelial system.

*Statistically significant difference ($P < 0.05$) compared with meloxicam.

†One infection and one abscess.

Both were considered to be possibly causally related to treatment with naproxen.

Global tolerance. Both patients and investigators rated meloxicam better than naproxen in global tolerance assessments. Mean global tolerance assessments by patients throughout the whole trial were 1.0 ± 1.3 cm for meloxicam and 1.1 ± 1.4 cm for naproxen, with corresponding values for investigators of 0.8 ± 1.1 and 1.0 ± 1.4 cm, respectively.

'Last value' observations of global tolerance, which included patients withdrawn prematurely from the study, showed a similar trend: 1.9 ± 2.6 and 2.4 ± 3.0 cm in the meloxicam and naproxen groups, respectively. Similar values were again given by investigators: 1.8 ± 2.6 and 2.3 ± 3.0 cm respectively.

The effects of demographic characteristics and concomitant therapy were assessed and it was found that patients who had suffered from RA for >8 years had the worst global tolerance of the trial drugs.

Laboratory parameters

In the naproxen-treated group, mean values for haemoglobin, erythrocytes and haematocrit decreased significantly from baseline values. There was no significant decrease in these parameters in the meloxicam-treated group and the difference between the two groups was significant for the decrease in haemoglobin ($P = 0.025$).

Mean serum creatinine showed a significant difference between the treatment groups ($P = 0.03$), with meloxicam-treated patients demonstrating a decrease and naproxen-treated patients an increase in mean values. The same pattern was observed for the mean serum urea values, with a significant difference between the groups ($P = 0.01$).

DISCUSSION

Most patients in this study had received previous treatment with NSAIDs, including naproxen, and almost 70% were receiving second-line therapies at the start of the study. The primary endpoints of efficacy show that meloxicam has a potent anti-inflammatory and analgesic action. There was a significant decrease in the number of painful/tender joints and in the number of swollen joints from the start of treatment. Both investigators and patients rated global efficacy of meloxicam and naproxen well on the VAS. There was no significant difference between the two treatments in the primary efficacy endpoints. Although there was a trend in favour of naproxen, the results for meloxicam compared well with those achieved with naproxen.

The secondary efficacy endpoints also displayed a significant improvement with both meloxicam and naproxen compared with baseline (with the exception of ESR in the naproxen-treated group). Most variables showed no significant difference between the two treatment groups. However, there was a significant difference in favour of naproxen with respect to the swollen joint index and the number of patients withdrawing due to lack of efficacy.

The results of this study are comparable with other trials of meloxicam in RA, in which a dose of 15 mg was also investigated. In a comparative study with piroxicam [15], meloxicam 15 mg showed similar efficacy to piroxicam 20 mg but with a lower incidence of adverse effects. In a placebo-controlled study [16], both meloxicam 15 mg and 7.5 mg were more effective than placebo, with a trend in favour of meloxicam 15 mg. Safety was comparable between the two meloxicam doses.

As expected, GI disturbances were the most frequently reported adverse events in both groups. These GI disturbances are thought to be caused by inhibition of prostaglandin biosynthesis, thereby interfering with the role of prostaglandins in gastric mucosal defence systems [17, 18]. This effect has been demonstrated by patients on naproxen in a recent study [19]. The number of adverse events and withdrawals due to GI disturbances were significantly greater in the naproxen-treated group and two cases of upper GI ulcer were reported. Similarly, significant decreases in mean values of haemoglobin, erythrocytes and haematocrit occurred in this group, suggesting higher GI blood loss with naproxen.

NSAIDs also inhibit prostaglandin synthesis in the kidney, which results in an increase in plasma urea and creatinine and, in extreme cases, renal failure [20]. Renal prostaglandins function to increase renal blood flow and the loss of urinary electrolytes and water. They also counteract the adverse events that occur when the renin–angiotensin system is stimulated or when catecholamines are released [21]. Without these compensatory mechanisms adverse reactions are more likely to occur. In this study there was a significant difference between the treatment groups regarding both the plasma creatinine and plasma urea results. The mean values of both parameters increased in the naproxen group but decreased in the meloxicam-treated patients when compared with the baseline results before the washout stage. This suggests that, at the doses used in this study, meloxicam may have less effect on renal prostaglandins than naproxen.

These results are in accord with the current view on selective COX-2 inhibition. Meloxicam as a COX-2 inhibitor shows a favourable safety profile on the GI tract and the renal system, as expected due from its low inhibition of COX-1.

In conclusion, the COX-2 inhibitor meloxicam shows promise as a treatment in RA. Meloxicam's efficacy in a dosage of 7.5 mg seems comparable to that of naproxen 750 mg, although there was a non-significant trend in favour of naproxen. Meloxicam 7.5 mg has the advantage of a lower incidence of side-effects, including a significantly lower incidence of GI and renal disturbances.

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NOTICE OF OFFICE PLAN TO CEASE SUPPLYING COPIES OF CITED U.S. PATENT REFERENCES WITH OFFICE ACTIONS, AND PILOT TO EVALUATE THE ALTERNATIVE OF PROVIDING ELECTRONIC ACCESS TO SUCH U.S. PATENT REFERENCES

Summary

The United States Patent and Trademark Office (Office or USPTO) plans in the near future to: (1) cease mailing copies of U.S. patents and U.S. patent application publications (US patent references) with Office actions except for citations made during the international stage of an international application under the Patent Cooperation Treaty and those made during reexamination proceedings; and (2) provide electronic access to, with convenient downloading capability of, the US patent references cited in an Office action via the Office's private Patent Application Information Retrieval (PAIR) system which has a new feature called "E-Patent Reference." Before ceasing to provide copies of U.S. patent references with Office actions, the Office shall test the feasibility of the E-Patent Reference feature by conducting a two-month pilot project starting with Office actions mailed after December 1, 2003. The Office shall evaluate the pilot project and publish the results in a notice which will be posted on the Office's web site (www.USPTO.gov) and in the Patent Official Gazette (O.G.). In order to use the new E-Patent Reference feature during the pilot period, or when the Office ceases to send copies of U.S. patent references with Office actions, the applicant must: (1) obtain a digital certificate from the Office; (2) obtain a customer number from the Office, and (3) properly associate applications with the customer number. The pilot project does not involve or affect the current Office practice of supplying paper copies of foreign patent documents and non-patent literature with Office actions. Paper copies of references will continue to be provided by the USPTO for searches and written opinions prepared by the USPTO for international applications during the international stage and for reexamination proceedings.

Description of Pilot Project to Provide Electronic Access to Cited U.S. Patent References

On December 1, 2003, the Office will make available a new feature, E-Patent Reference, in the Office's private PAIR system, to allow more convenient downloading of U.S. patents and U.S. patent application publications. The new feature will allow an authorized user of private PAIR to download some or all of the U.S. patents and U.S. patent application publications cited by an examiner on form PTO-892 in Office actions, as well as U.S. patents and U.S. patent application publications submitted by applicants on form PTO/SB08 (1449) as part of an IDS. The retrieval of some or all of the documents may be performed in one downloading step with the documents encoded as Adobe Portable Document format (.pdf) files, which is an improvement over the current page-by-page retrieval capability from other USPTO systems.

Steps to Use the New E-Patent Reference Feature During the Pilot Project and Thereafter

Access to private PAIR is required to utilize E-Patent Reference. If you don't already have access to private PAIR, the Office urges practitioners, and applicants not represented by a practitioner, to take advantage of the transition period to obtain a no-cost USPTO Public Key Infrastructure (PKI) digital certificate, obtain a USPTO customer number, associate all of their pending and new application filings with their customer number, install no-cost software (supplied by the Office) required to access private PAIR and E-Patent Reference feature, and make appropriate arrangements for Internet access. The full instructions for obtaining a PKI digital certificate are available at the Office's Electronic Business Center (EBC) web page at: <http://www.uspto.gov/ebc/downloads.html>. Note that a notarized signature will be required to obtain a digital certificate.

To get a Customer Number, download and complete the Customer Number Request form, PTO-SB125, at: http://www.uspto.gov/web/forms/sb0125.pdf. The completed form can then be transmitted by facsimile to the Electronic Business Center at (703) 308-2840, or mailed to the address on the form. If you are a registered attorney or patent agent, then your registration number must be associated with your customer number. This is accomplished by adding your registration number to the Customer Number Request form. A description of associating a customer number with an application is described at the EBC web page at: http://www.uspto.gov/ebc/registration_pair.html.

The E-Patent Reference feature will be accessed using a new button on the private PAIR screen. Ordinarily all of the cited U.S. patent and U.S. patent application publication references will be available over the Internet using the Office's new E-Patent Reference feature. The size of the references to be downloaded will be displayed by E-Patent Reference so the download time can be estimated. Applicants and registered practitioners can select to download all of the references or any combination of cited references. Selected references will be downloaded as complete documents as Adobe Portable Document Format (.pdf) files. For a limited period of time, the USPTO will include a copy of this notice with Office actions to encourage applicants to use this new feature and, if needed, to take the steps outlined above in order to be able to utilize this new feature during the pilot and thereafter.

During the two-month pilot, the Office will evaluate the stability and capacity of the E-Patent Reference feature to reliably provide electronic access to cited U.S. patent and U.S. patent application publication references. While copies of U.S. patent and U.S. patent application publication references cited by examiners will continue to be mailed with Office actions during the pilot project, applicants are encouraged to use the private PAIR and the E-Patent Reference feature to electronically access and download cited U.S. patent and U.S. patent application publication references so the Office will be able to objectively evaluate its performance. The public is encouraged to submit comments to the Office on the usability and performance of the E-Patent Reference feature during the pilot. Further, during the pilot period registered practitioners, and applicants not represented by a practitioner, are encouraged to experiment with the feature, develop a proficiency in using the feature, and establish new internal processes for using the new access to the cited U.S. patents and U.S. patent application publications to prepare for the anticipated cessation of the current Office practice of supplying copies of such cited

references. The Office plans to continue to provide access to the E-Patent Reference feature during its evaluation of the pilot.

Comments

Comments concerning the E-Patent Reference feature should be in writing and directed to the Electronic Business Center (EBC) at the USPTO by electronic mail at eReference@uspto.gov or by facsimile to (703) 308-2840. Comments will be posted and made available for public inspection. To ensure that comments are considered in the evaluation of the pilot project, comments should be submitted in writing by January 15, 2004.

Comments with respect to specific applications should be sent to the Technology Centers' customer service centers. Comments concerning digital certificates, customer numbers, and associating customer numbers with applications should be sent to the Electronic Business Center (EBC) at the USPTO by facsimile at (703) 308-2840 or by e-mail at EBC@uspto.gov.

Implementation after Pilot

After the pilot, its evaluation, and publication of a subsequent notice as indicated above, the Office expects to implement its plan to cease mailing paper copies of U.S. patent references cited during examination of non provisional applications on or after February 2, 2004; although copies of cited foreign patent documents, as well as non-patent literature, will still be mailed to the applicant until such time as substantially all applications have been scanned into IFW.

For Further Information Contact

Technical information on the operation of the IFW system can be found on the USPTO website at http://www.uspto.gov/web/patents/ifw/index.html. Comments concerning the E-Patent Reference feature and questions concerning the operation of the PAIR system should be directed to the EBC at the USPTO at (866) 217-9197. The EBC may also be contacted by facsimile at (703) 308-2840 or by e-mail at EBC@uspto.gov.

Date. 12/1/03

Nicholas P. Godici

Nicholas P. Godici
Commissioner for Patents

USPTO TO PROVIDE ELECTRONIC ACCESS TO CITED U.S. PATENT REFERENCES WITH OFFICE ACTIONS AND CEASE SUPPLYING PAPER COPIES

In support of its 21st Century Strategic Plan goal of increased patent e-Government, beginning in June 2004, the United States Patent and Trademark Office (Office or USPTO) will begin the phase-in of its E-Patent Reference program and hence will: (1) **provide downloading capability of the U.S. patents and U.S. patent application publications cited in Office actions** via the E-Patent Reference feature of the Office's Patent Application Information Retrieval (PAIR) system; and (2) **cease mailing paper copies of U.S. patents and U.S. patent application publications with Office actions** (in applications and during reexamination proceedings) except for citations made during the international stage of an international application under the Patent Cooperation Treaty (PCT). In order to use the new E-Patent Reference feature applicants must: (1) obtain a digital certificate and software from the Office; (2) obtain a customer number from the Office; and (3) properly associate patent applications with the customer number. Alternatively, copies of all U.S. patents and patent application publications can be accessed without a digital certificate from the USPTO web site, from the USPTO Office of Public Records, and from commercial sources. The Office will continue the practice of supplying paper copies of foreign patent documents and non-patent literature with Office actions. Paper copies of cited references will continue to be provided by the USPTO for international applications during the international stage.

Schedule

June 2004	TCs 1600, 1700, 2800 and 2900
July 2004	TCs 3600 and 3700
August 2004	TCs 2100 and 2600

All U.S. patents and U.S. patent application publications are available on the USPTO web site. However, a simple system for downloading the cited U.S. patents and patent application publications has been established for applicants, called the E-Patent Reference system. As E-Patent Reference and Private PAIR require participating applicants to have a customer number, retrieval software and a digital certificate, all applicants are strongly encouraged to contact the Patent Electronic Business Center to acquire these items. To be ready to use this system by June 1, 2004, contact the Patent EBC as soon as possible by phone at 866-217-9197 (toll-free), 703-305-3028 or 703-308-6845 or electronically via the Internet at ebc@uspto.gov.

Other Options

The E-Patent Reference function requires the applicant to use the secure Private PAIR system, which establishes confidential communications with the applicant. Applicants using this facility must receive a digital certificate, as described above. Other options for obtaining patents which do not require the digital certificate include the USPTO's free Patents on the Web program (http://www.uspto.gov/patft/index.html). The USPTO's Office of Public Records also supplies copies of patents for a fee (http://ebiz1.uspto.gov/oems25p/index.html). Commercial sources also provide U.S. patents and patent application publications.

For complete instructions see the Official Gazette Notice, USPTO TO PROVIDE ELECTRONIC ACCESS TO CITED U.S. PATENT REFERENCES WITH OFFICE ACTIONS AND CEASE SUPPLYING PAPER COPIES, on the USPTO web site.